NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Holoclar for treating limbal stem cell deficiency after eye burns

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Holoclar for treating limbal stem cell deficiency after eye burns [ID899]

**Contents:**



*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# Pre-meeting briefing
# Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

# Key issues – clinical

- Has the clinical effectiveness of Holoclar been adequately demonstrated?
  - Clinical effectiveness from low quality case-series data
  - Company conduct hypothesis testing; study not designed for this
  - Low patient numbers, although relatively high given rare disease
  - Case-series for Italian patients – is this generalisable to UK?
  - Only 1 patient had bilateral disease – can any judgements be made about bilateral effectiveness?
  - Comparator data also small numbers and low quality – can any judgements about comparative effectiveness be made?
- Should comparator data be pooled?
  - Company and ERG agree that comparator data cannot be pooled in clinical section, but company pool data for model
- Can Holoclar be considered innovative? If so does committee need to take account of this in its recommendations?
  - Holocar won UK Prix Galien Orphan Product award for innovation
  - Regenerative medicine – have all the benefits of treatment be quantified?

2

# Key issues – cost

- All treatments including Holoclar are dominated by CLAU (that is, are more expensive/less effective)
- Effectiveness assumptions based on weak evidence (case series data) – are assumptions appropriate for decision making?
- Are bilateral results valid?
  - Is it appropriate to assume bilateral effectiveness same as unilateral?
  - Bilateral effectiveness data available for only 1 patient
- No utility values for this condition – have company used appropriate sources? Which assumptions are more plausible, company or ERG?
- Should company have used discount rate of 1.5% or 3.5%?
- What are the most plausible assumptions about autologous serum eye drops (used post-operatively for Holoclar, and used for flare-ups)?
- Would patients with unilateral LSCD be offered a second procedure after failure of CLAL?
- Are company assumptions about failure rates plausible?
- Which cost-effectiveness results are most plausible – company or ERG?

3

# Abbreviations

- Cd-CLAL - Conjunctival limbal allograft from a cadaveric donor
- Lr-CLAL - Conjunctival limbal allograft from a living relative donor
- CLAU - Conjunctival limbal autograft
- KLAL - Keratolimbal allograft
- LSCD - Limbal stem cell deficiency
- VA – Visual acuity

4

# Definitions

| | |
|---|---|
| Limbal stem cells | Stem cells for the cornea which reside at the corneoscleral limbus |
| Limbal stem cell deficiency | Limbal stem cells may be partially or totally depleted with resulting abnormalities in the corneal surface. |
| Allograft | Transplant from one person to another |
| Autograft | A tissue or an organ grafted into a new position in or on the body of the same individual. |
| Keratoplasty | Cornea transplant or corneal graft |
| Oculoplastic interventions | Plastic and reconstructive surgery on the eye |
| Keratolimbal allograft | Transplanting limbal epithelial stem cells of the cornea from a cadaveric donor. |
| Ex vivo expansion | Tissue grown in an external environment |

5

# NICE decision problem

| NICE scope and company submission | ERG comment |
|---|---|
| **Population**<br>Adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2mm$^2$ of undamaged limbus | Agree. But no clinical evidence presented for bilateral |
| **Intervention**<br>Ex vivo expanded autologous human corneal epithelial cells containing stem cells | Agree |

6

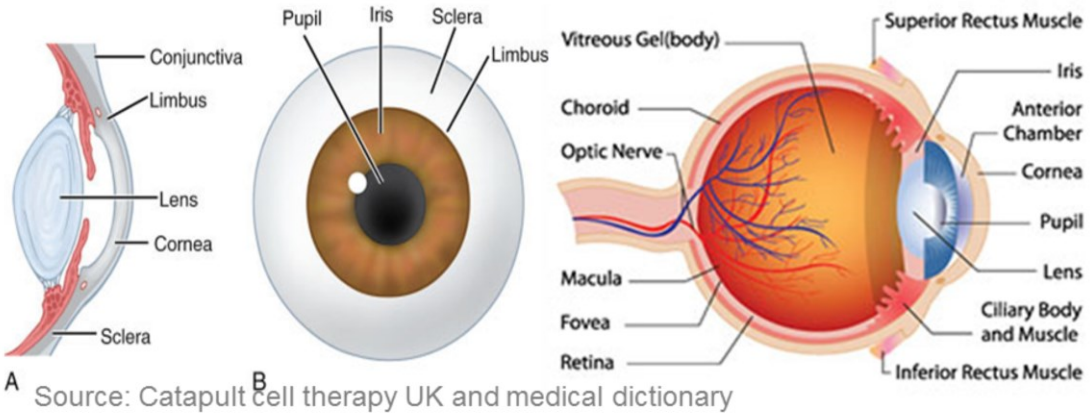
# Decision problem (1)

| NICE scope and company submission | ERG comment |
|---|---|
| **Comparators**<br>For people with unilateral LSCD<br>• conjunctival limbal autograft<br>• best supportive care<br>For people with bilateral LSCD<br>• conjunctival limbal autograft<br>• limbal epithelial stem cells allografts<br>• Best supportive care | • Unilateral LSCD: limbal epithelial stem cells *allograft* (e.g. CLAL, KLAL) **is** relevant comparator<br>• Bilateral LSCD: Conjunctival limbal *autograft* (CLAU) **not** appropriate comparator. |
| **Outcomes**<br>• clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation<br>• symptoms of LSCD including pain, burning and photophobia<br>• Visual acuity (the affected eye)<br>• Visual acuity (the whole person)<br>• Adverse events<br>• Health related quality of life (HRQoL) | • No HRQoL data presented in clinical section of company submission |

7

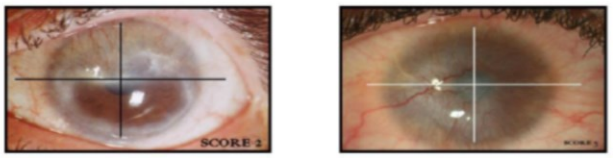
# Disease background (1)

**Figure: Anatomy of eye**




Source: Catapult cell therapy UK and medical dictionary

**Figure: Moderate and severe LSCD**



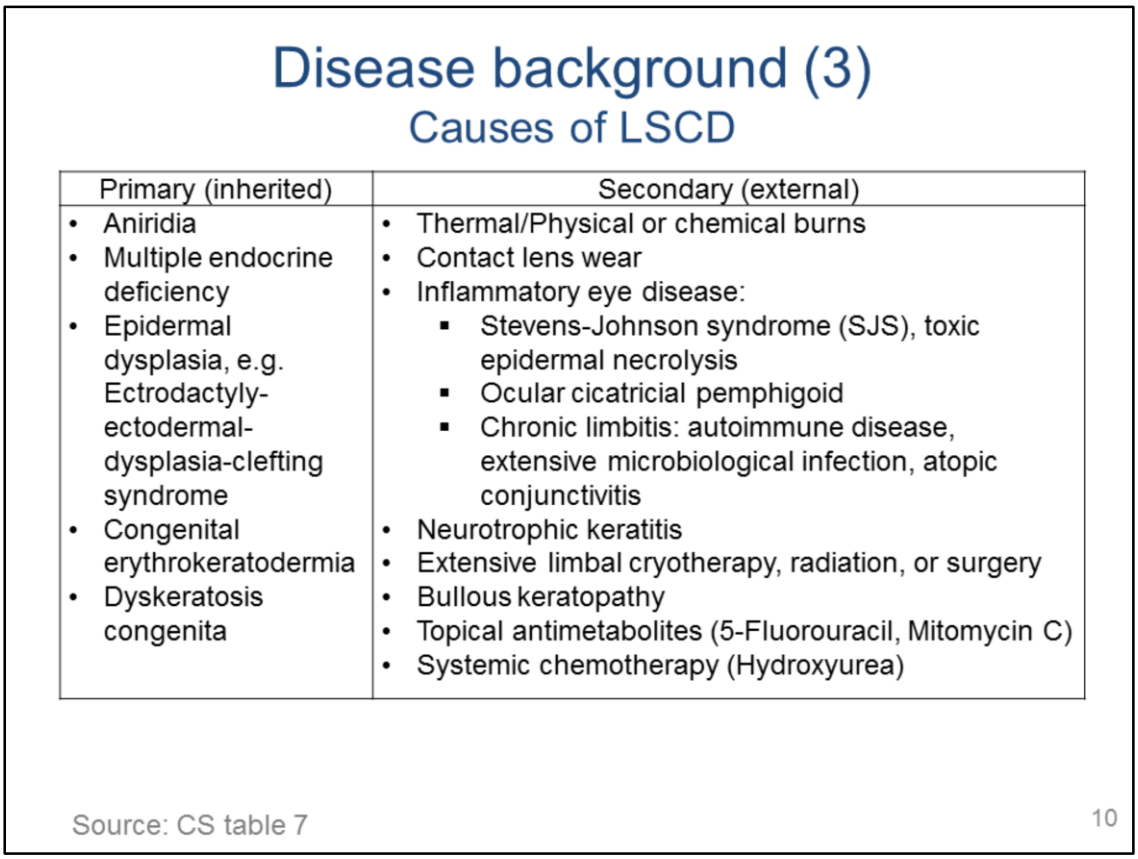
Moderate LSCD | Severe LSCD

8

# Disease background (2)

- Cornea – clear, rigid layer covering front of eye. Divided in 4 quadrants: superior, temporal, inferior and nasal.
- Cells on cornea surface constantly renewed and replaced by limbal stem cells.
- Damage to source of limbal stem cells from either external (e.g. chemical or physical burns) or inherited causes can cause limbal stem deficiency (LSCD), affects renewal and replacement
- Can lead to cornea being repaired by different types of eye cell and excessive ingrowth of blood vessels (neovascularisation)
- Can cause opaque cornea, impaired vision, chronic pain and burning, and photophobia
- Treatment aims to restore healthy surface
- Prevalence of LSCD in Europe is 0.3 per 10,000 people.
- In the UK incidence of LSCD due to severe chemical corneal injury is 0.02 per 100,000 in patients

9



# Disease background (3)

## Causes of LSCD

| Primary (inherited) | Secondary (external) |
|---|---|
| • Aniridia<br>• Multiple endocrine deficiency<br>• Epidermal dysplasia, e.g. Ectrodactyly-ectodermal-dysplasia-clefting syndrome<br>• Congenital erythrokeratodermia<br>• Dyskeratosis congenita | • Thermal/Physical or chemical burns<br>• Contact lens wear<br>• Inflammatory eye disease:<br>▪ Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis<br>▪ Ocular cicatricial pemphigoid<br>▪ Chronic limbitis: autoimmune disease, extensive microbiological infection, atopic conjunctivitis<br>• Neurotrophic keratitis<br>• Extensive limbal cryotherapy, radiation, or surgery<br>• Bullous keratopathy<br>• Topical antimetabolites (5-Fluorouracil, Mitomycin C)<br>• Systemic chemotherapy (Hydroxyurea) |

Source: CS table 7

10

LSCD is characterised by a loss or deficiency of the progenitor stem cells located in the limbus that are vital for re-population of the corneal epithelium and to the barrier function of the limbus.

When these stem cells are lost, the corneal epithelium is unable to repair and renew itself. This results in epithelial breakdown and recurrent or persistent epithelial defects, conjunctivalisation of the corneal surface with neovascularisation, chronic inflammation and corneal scarring.

All of these contribute to loss of corneal transparency, potential visual loss, chronic pain and burning, photophobia and keratoplasty failure. In severe LSCD, part of the cornea, usually including the pupillary area, is covered by a thick fibrovascular pannus.

LCSD may result from direct injury to the limbal stem cells, destruction of the limbal stem cell niche, or both

It can be caused by a wide variety of primary (inherited) and secondary (external) and more rarely there are idiopathic (unknown) causes.

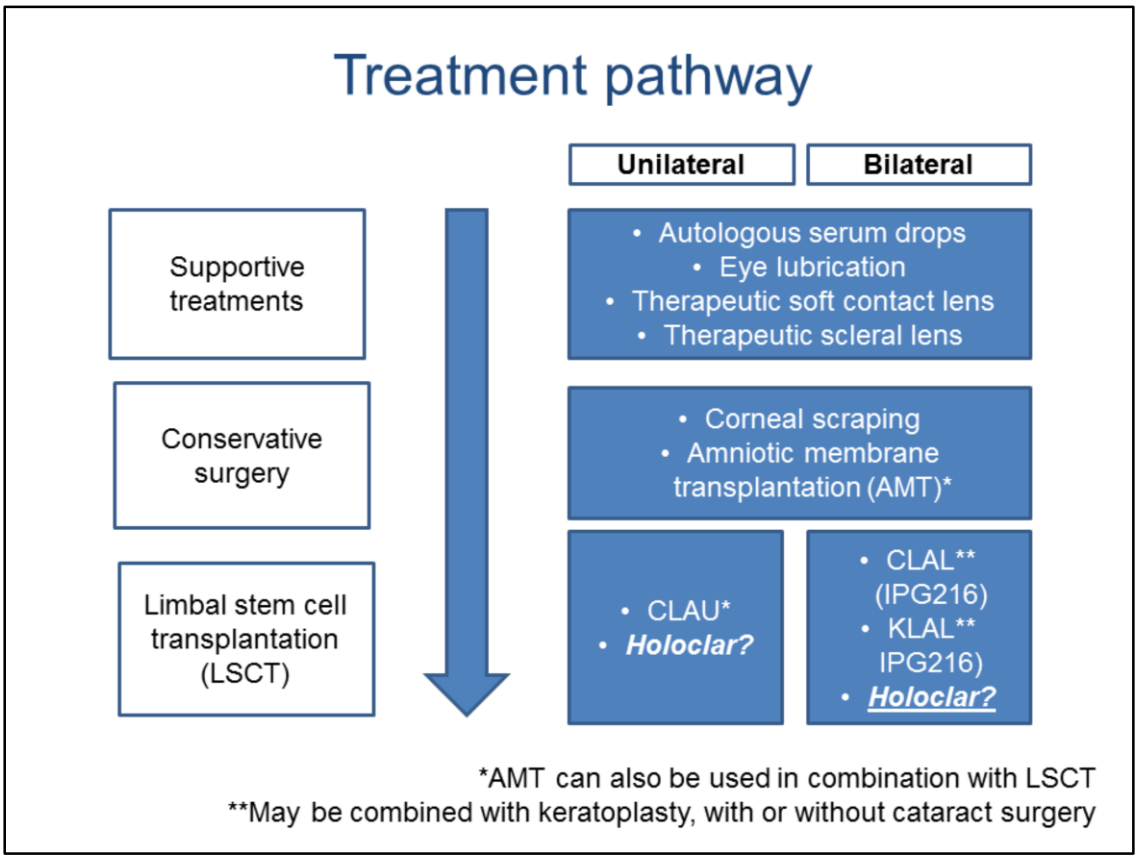
## Technology

| | |
|---|---|
| Marketing authorisation (**conditional** on on-going phase IV prospective uncontrolled interventional study HLSTM0350 (or HOLOCORE), expected 2020. | Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 $mm^2$ of undamaged limbus is required for biopsy. |
| Administration method | Administered by implantation of transplant. |
| Cost | List price (all-inclusive e.g. staff training, shipment of biopsy etc.) is £80,000 (ex VAT) per treatment per eye. (Has PAS, reduces cost to [redacted]) |

11

The cost includes:

- A full training program for surgeon and NHS staff.
- Shipment of the biopsy from the treatment centre to the production facility under controlled conditions.
- Storage of the biopsy in a controlled environment and according to strict privacy-protecting Standard Operating Procedures.
- Freezing and storage of the biopsy, giving the potential for a second Holoclar to be manufactured from the same biopsy.
- Ex-vivo GMP culturing and expansion of the biopsy cells, testing for potency and approval under conditions of Good Laboratory Practice.
- Shipment and delivery of the final product to the treatment centre under controlled conditions.




The company stated that the proposed use of Holoclar in adults with moderate to severe LSCD, unilateral or bilateral, due to physical or chemical ocular burns is as follows:

For unilateral LSCD, as an alternative to CLAU in patients who are unsuitable for CLAU or who are unwilling to undergo CLAU due to concerns about damage to their contralateral healthy donor eye or in whom CLAU has failed and cannot therefore be repeated.

For bilateral LSCD where patients have a minimum of 1-2 mm2 of undamaged limbus:

- as an alternative to KLAL in patients who do not have an available and/or willing live-related donor;
- as an alternative to Ir-CLAL and KLAL in patients for whom topical and systemic immunosuppression is considered unsuitable or is undesirable; and/or
- as an alternative to Ir-CLAL and KLAL in patients who require the potential for a successful treatment outcome beyond 3-5 years.

It stated that this proposed introduction of Holoclar does not alter the structure of the current clinical pathway within the NHS, but provides an alternative treatment option for the patient groups referred to above.

### Current management

The company stated that the hierarchy of current treatment for LSCD varies from symptom control using conservative measures to surgical intervention involving the transplantation of viable epithelial 'stem' cells. Measures of treatment success include the a stable ocular surface (OS) (that is, transparency, no superficial corneal vascularisation, no conjunctivalisation and no epithelial irregularity, defects or breakdown), improvements in vision, pain and photophobia.

The company stated that conservative therapeutic options include supportive management, corneal scraping, and amniotic membrane transplantation (AMT). In partial LSCD, recovery depends on the presence of some remaining limbal epithelial stem cells (LESCs) that can be rehabilitated to restore the epithelium. In total LSCD, where there are no remaining stem cell reserves, the cornea may be reseeded with new LESCs using sections of donor tissue either from the patient's fellow eye (autograft, CLAU) or from a living-related or cadaveric donor (LRD or CD) (allograft: CLAL, KLAL) in a procedure known as LSCT.

### Supportive management

Includes OS lubrication to prevent epithelial adhesion to the tarsal conjunctiva and reduce shear stress. Autologous serum drops also promote migration and proliferation of healthy epithelium. Therapeutic soft contact lenses may be used to promote healing of persistent epithelial defect (PED) and prevent the formation of new defects. Therapeutic scleral lenses also may improve vision and reduce pain and photophobia.

### Conservative surgical options

#### *Corneal scraping*

Corneal scraping aims to remove overgrown conjunctiva, to enable re-epithelialisation by islands of functioning corneal epithelial stem cells. The company stated it may be necessary to repeat the procedure 2 to 3 times because the conjunctival epithelium migrates more rapidly than the corneal epithelium.

#### *Amniotic membrane transplantation (AMT)*

The amniotic membrane is an immunologically inert, semi-transparent tissue from the inner part of the placenta. An AMT promotes proliferation and migration of residual LESCs and a reduction of inflammatory reactions. This promotes a healthy epithelium with reduced corneal NV and contributes to the recovery of the corneal surface, improved VA, and alleviation of pain and photophobia. An AMT may be performed immediately after corneal scraping as the overgrown conjunctiva is removed and the amnion membrane is patched over the epithelial defect. However, variations in the biological source of the membrane may affect clinical outcomes and there is a theoretical risk of disease transmission hence serological screening of the donor's blood for syphilis, human immunodeficiency virus, and hepatitis virus B and C should be conducted before

use.

The use of AMT is considered a useful adjunct to LSCT procedures in an attempt to promote healing and has been used alone or in combination with CLAU, CLAL and KLAL to aid OS reconstruction in patients with chronic chemical burns.

**Invasive surgical techniques**

***Limbal stem cell transplantation***

LSCT may be performed by **CLAU**, **CLAL** or **KLAL** procedures. The differences between the 3 transplant techniques are related to the source of the donor stem cells and the carrier tissue used to transfer stem cells. Carrier tissue is needed in limbal transplantation because it is not possible to transfer limbal stem cells alone. Holoclar is a non-standard type of CLAU

Both CLAU and CLAL use the conjunctiva as the carrier tissue but differ in their source of limbal stem cells:

- CLAU: autologous graft derived from the patient's healthy eye, transplanted using a conjunctiva carrier
- CLAL: allogeneic graft derived from a consenting living related donor, transplanted using a conjunctiva carrier
- KLAL: allogeneic graft derived from a cadaveric donor, transplanted using the cornea as carrier tissue.

The company stated that CLAU, CLAL and KLAL have been associated with significant challenges that may prevent patients from undergoing these procedures. These challenges include the need for large amounts of limbal tissue, which can risk inducing LSCD in the donor eye, and in cases of allogeneic tissue, the requirement of potent immune suppression that can pose the risk of life-threatening opportunistic infections and neoplasia. It stated that unilateral or partial LSCD can be treated by transplantation of *autologous* limbal stem cells from the healthy to the diseased eye. However, if bilateral LSCD occurs, the treatment relies on the transplantation of *allogeneic* limbal stem cells.

The company stated that there is uncertainty regarding the best surgical management of LSCD. The procedure choice may be based on several factors, including the presence of bilateral or unilateral disease, the extent of the LSCD, patient expectations and acceptance of the procedure, risk to a healthy eye, and the availability and willingness of a living related donor (LRD). The risk of LSCT failure increases if the recipient has external eye diseases such as dry eye, eyelid or lid margin abnormalities, extensive conjunctival metaplasia, keratinisation, corneal anaesthesia, tear film abnormalities,

mucus depletion, and chronic inflammation.

**CLAU (note: Holoclar is a non-standard type of CLAU)**

- Autograft from patient's healthy eye.
- Unsuitable for bilateral LSCD.
- No immunosuppression required (as tissue is sourced from patient's healthy eye)
- Requires large section of limbal tissue. Minimum 4-6 mm2 of limbal tissue superiorly and inferiorly (minimum 8-12 mm2 total) is dissected from the patients other healthy eye and transplanted using a conjunctiva carrier. This risks inducing LSCD in donor eye.

The company stated that the requirement to remove a large section of limbal tissue from the only seeing fellow eye may be an unacceptable risk for some patients, who may decline the procedure, and if this procedure fails it cannot be repeated as the patient's healthy eye cannot be used again to donate conjunctivo limbal tissue. The company stated that despite this concern, reports regarding subsequent stem cell deficiency in a healthy donor eye are very rare and when patients are selected appropriately it is a generally well-tolerated and uneventful procedure.

Complications of this procedure include bleeding, viral/bacterial infection, inflammation, PED, corneal thinning, corneal melting, ulceration, perforation, glaucoma and recurrence of LSCD with progressive corneal conjunctivalisation. Other complications that may occur are related to the transplanted limbal graft (size, thickness, position and alignment) and chronic OS exposure.

**CLAL**

- Allograft from LRD or CD.
- Suitable for bilateral LSCD.
- Requires systemic immunosuppression.
- Minimum 4-6 mm2 of limbal tissue superiorly and inferiorly (minimum 8-12 mm2 total) is dissected from the LDR donor eye and transplanted using a conjunctiva carrier.
- Risk of disease transmission and neoplasia.
- Risk of inducing LSCD in LRD eye.

Immunosuppression varies but usually consists of a combination of topical and systemic agents e.g. prednisone, cyclosporine A, azathioprine, and dexamethasone. Some protocols involve on-going immunosuppression while others taper and eliminate immunosuppression after 1 or 2 years.

The company stated that a disadvantage of CLAL is the limited amount of tissue that can be donated for transplantation (the procedure for LSC donation is essentially the same as that for CLAU except in a LRD rather than the patient's healthy eye). Therefore, in severe total LSCD, transplanted limbal stem cells may be unable to sustain sufficient long-term epithelial cell production for the entire limbus. Another disadvantage is the possibility of induced stem cell deficiency in the donor. CLAL also comes with an increased risk of transmitting infectious disease and promoting neoplasia due to the long-term use of immunosuppressants, hence serological screening of the donor's blood for syphilis, human immunodeficiency virus, and hepatitis virus B and C is required before transplantation occurs. Furthermore, some surgeons in England do not offer lr-CLAL due to the high failure rate and potential compromise to the donor.

**KLAL**

- Allograft from CD.
- Suitable for bilateral LSCD.
- Requires systemic immunosuppression.
- Entire CD limbus can be transplanted using the cornea as carrier tissue.
- Risk of disease transmission and neoplasia.
- Risk of inducing LSCD in LRD eye.

The company stated that this option is particularly suited to patients with total bilateral LSCD, especially when a LRD is unavailable. There is a need for a large section of the limbal tissue. However, an advantage of the KLAL procedure is that the entire cadaveric donor) (CD) limbus can be transplanted, and in practice a 360-degree lamellar ring that consists of the entire donor eye's limbus, most of the peripheral cornea and a minimal portion of the scleral tissue is used. However, whilst in theory more limbal stem cells can be obtained from a CD than a live donor, the lengthy preservation time needed for HLA antigen matching results in limbal stem cell dropout.

Although HLA matching is advisable it is almost impossible to obtain immune histocompatibility between the recipient and the donor cadaver, hence systemic and topical immunosuppression is required. Furthermore, there is also evidence that LRD allografts fare better than CD allografts possibly due to the partial HLA matching between recipient and the LRD, as well as the increased expected viability of tissue retrieved from LRDs.

A drawback of KLAL is that it takes several weeks to achieve entire corneal surface epithelialisation from the CD graft, and in some cases, full epithelialisation may not occur. There is also a theoretical risk of disease transmission, hence serological screening of the donor's blood for syphilis, human immunodeficiency virus, and hepatitis virus B and C should be conducted before use. In addition formation of neoplasia secondary to immunosuppression may need to be considered.

AEs including a reduction in VA from baseline and the development of glaucoma have been reported after KLAL.

The risk of graft rejection after KLAL is high, because the limbal tissue is highly vascularised, highly antigenic and rich in Langerhans cells. Thus, postoperative management, which includes immunosuppression, is very important in prolongation of graft survival. For success, KLAL with immunosuppression may need to be repeated more than once.

Risk factors such as keratinisation, inflammation, and dry eye and symblepharon have been implicated for KLAL failure. It is recommended that symblepharon should be surgically corrected prior to KLAL procedure. Inflammation and postoperative infection may be triggered by use of sutures; they can be vascularised and may provoke graft rejection. The use of fibrin sealants instead of sutures in KLAL surgery may decrease the risk of rejection.

**Adjunctive surgical procedures**

All the LSCT surgical options may be combined with penetrating keratoplasty (PKP) or dep anterior lamellar keratoplasty (DALK), with or without cataract surgery. PKP and DALK are used to treat corneal stromal scarring that may persist in patients with ocular burns even after the LSCD has been corrected. PKP involves a full-thickness corneal graft, whilst DALK is a less invasive procedure that selectively replaces the anterior layer of the cornea down to Descemet's membrane leaving the endothelium intact.

PKP used alone in LSCD offers temporary restoration of corneal transparency as eventually conjunctival cells begin to invade and resurface the cornea.

The general health of the OS environment, with a good tear film layer and eyelid closure, is considered to be important for successful LSCT. If there is severe associated dryness and scarring of the OS, keratoprosthesis (replacing a diseased cornea with an artificial cornea) is considered to be the only option. The complications of a keratoprosthesis placement include infection, corneal melt, glaucoma, as well as formation of a retroprosthetic membrane. A Boston type I keratoprosthesis is suitable for high risk patients for corneal transplantation, such as those with repeated graft failure or severe OS disease and has been used in managing bilateral LSCD secondary to ocular burns.

# NICE guidance

- 'Corneal endothelial transplantation' (2009) NICE interventional procedures guidance 304
  - Current evidence on safety and efficacy is adequate to support the use of this procedure
- 'Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium' (2007) NICE interventional procedures guidance 216
  - Current evidence on safety and efficacy does not appear adequate for procedure to be used without special arrangements for consent and for audit or research

13

# Patient perspective (1)

- No patient expert submission available
- The company presented patient testimonials:
- After the accident:
  - *"It had a devastating effect on me. I lost my job and couldn't ride my mountain bike or go jet-skiing which I had enjoyed before. My eye was often in agony and would be weeping and red raw. If it was bad it meant I couldn't drive so it affected just about every aspect of my life. I had years of treatment but it was just trying different creams and ointments in a bid to stop the pain. None of them had any hope of restoring the sight."*
- After the treatment with Holoclar:
  - *"I never thought life would be this good again. I can never thank the doctors enough for restoring my sight. It's almost impossible to put into words what it means to me. I haven't just got my full sight back, I've got my life back. I'm working, I can go jet-skiing again and I also ride horses. I have my life back thanks to the operation."*

14

# Patient perspective (2)

- After the accident:
  - *"… They [doctors] said that the stem cells that live on the front of my eye and keep it clear had been damaged and that it was touch and go whether or not they would recover. They didn't and the front of my eye scarred and turned white. For three years I was blind in that eye. It looked awful too and I lost all of my self-confidence. I was resigned to spending the rest of my life like that."*
- After the treatment with Holoclar:
  - *"I could hardly believe it! I could see the top letter on the eye chart again! The graft had 'taken'. What was even better was the way my eye looked. No longer did I have a strange looking eye although it was still a little bloodshot from the operation. Over the following month my vision got better and better eventually returning to 100%. The redness went away too and you couldn't tell the difference between my two eyes! It was so fantastic being able to see again."*

15

# Clinical evidence

- No RCTs for Holoclar or comparator treatments

**Holoclar evidence:**

  - Primarily from 3 x Italian case series, moderate to severe unilateral or bilateral LSCD due to ocular burns
  - Main evidence from HLSTM01 (n=104) with supportive evidence from HLSTM02 (n=29) and HLSTM04 (n=15)

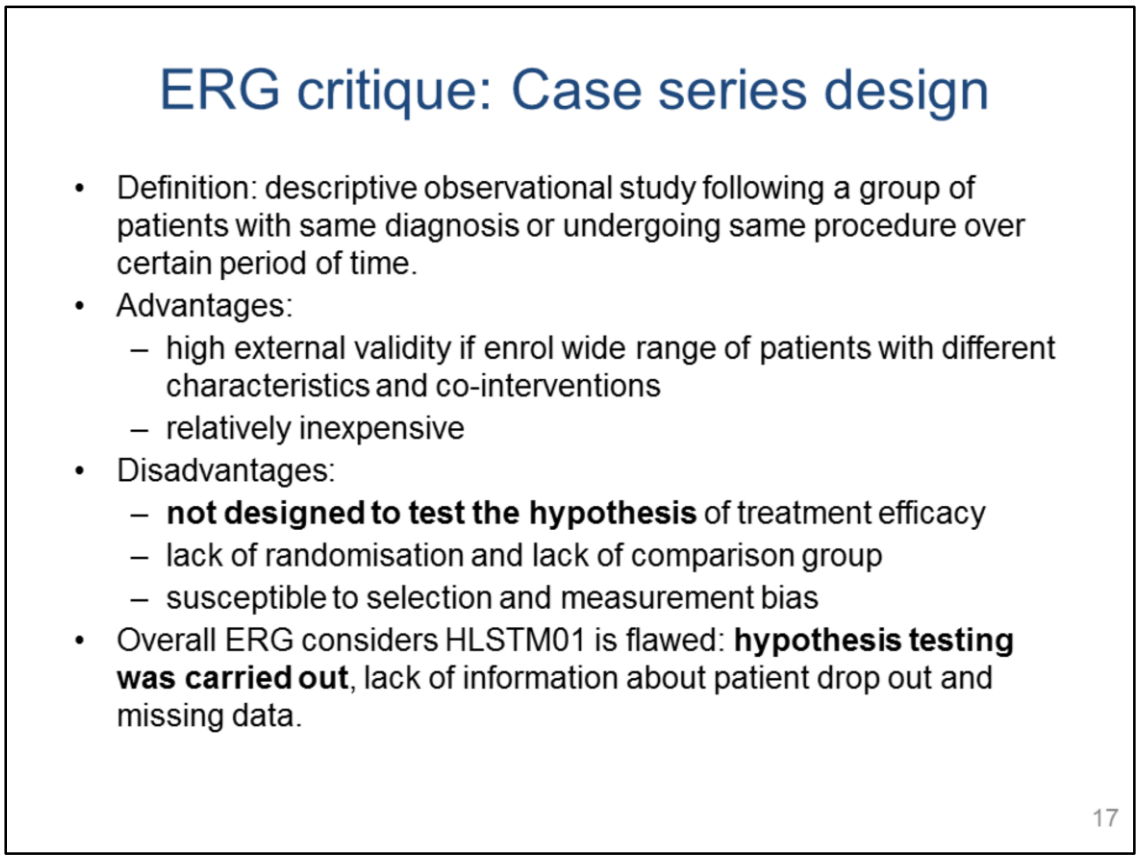
- Primary outcome HLSTM01: transplant success (based on stable corneal epithelium without significant recurrence of neo-vascularisation at 12 months post-intervention)
- Main secondary outcomes included symptom resolution (pain, burning and photophobia), inflammation, neovascularisation, visual acuity, number of successful keratoplasties after LSCT and safety.

**Comparator evidence:**

- 1 x randomised study of patients with unilateral LSCD treated with conjuctival limbal allograft from either living relative or cadaver (n=20)
- 22 other relevant studies, (n=1 to 78) all case studies or case series
- Inappropriate to combine studies because of heterogeneity

16

The clinical evidence section will focus on the results of HLSTM01




Overall ERG considers HLSTM01 is flawed: **hypothesis testing was carried out**, lack of information about patient drop out and missing data.

# Holoclar study characteristics (1)

- HLSTM01:
  - ITT population (n=104) patients treated with Holoclar and had control visit at least 6 months after transplantation.
  - Per protocol population (n=99)
- HLSTM01, 02 and 04:
  - Across all 3 studies, n=219. However, only 135 patients available for analyses, with data missing for 82 patients
  - Company stated that missing data did not negate conclusions of Holoclar because 25 of 82 missing patients were included in 2 other studies, which had similar results to HLSTM01/02

| **Table: HLSTM01 patient characteristics (n=104)** | |
|---|---|
| Mean age | 46.8 |
| Age range | 13.7 to 79.1 |
| Male n (%) | 80 (76.9) |
| Time from injury to treatment with Holoclar | 18.4 years |

Source: ERG report, p.45

18

Duration of follow up was 10 – 14.5 years, the main end-points were measured at 12 months.

# Holoclar study characteristics (2): ERG comments

- Given rarity of condition, study population substantial
- Clinical advice to ERG: study population representative of those who would be treated in the NHS
- Risk of bias from missing data
  - Exact number of missing cases unclear as company calculation (135 + 82) results in n=217, not 219
  - Company unable to provide reasons for non-participation
  - Company's attempt to address bias related to missing data is insufficiently robust to support conclusions about bias.

19

# HLSTM01 (1): study results

Primary outcome (transplant success):

- ITT population (including missing data imputed as failure: 75 patients (**72.1%**; 95% CI: 62.5 to 80.5%).

Secondary outcomes:

- Visual acuity: Improvement by at least one line:
  - All patients (n=104) 51 patients (**49%**; 95% CI: 39.4 to 58.6%)
  - Patients without stromal scarring (n=18): 15 patients (**83.3%**; 95% CI: 66.1 to 100%)
- Pain/burning/photophobia:

**Table: HLSTM01 Patients with LSCD symptoms pre and 12 months post surgery**

| | Pre-surgical assessment n (%) | 12 months post-surgery n (%) |
|---|---|---|
| Any symptoms | 40 (38.5) | 12 (11.5) |
| Pain | 7 (6.7) | 7 (6.7)* |
| Burning | 30 (28.8) | 7 (6.7) |
| Photophobia | 35 (33.7) | 8 (7.7) |
| * Based on 97 patients | | |

Source: ERG report, p.46

20

Transplant success defined as: composite endpoint of rate of patients with none or mild superficial corneal neovascularisation and none or trace epithelial defects.

Results of the sensitivity analysis excluding missing data were similar to ITT (75.8%; 95% CI: 66.1% to 83.8%). The company stated that a masked independent assessor evaluated the data that were available for each case at baseline and at 12 months (n=46) and results suggested that the treatment was a success in 31 out of 46 cases (67.4%).

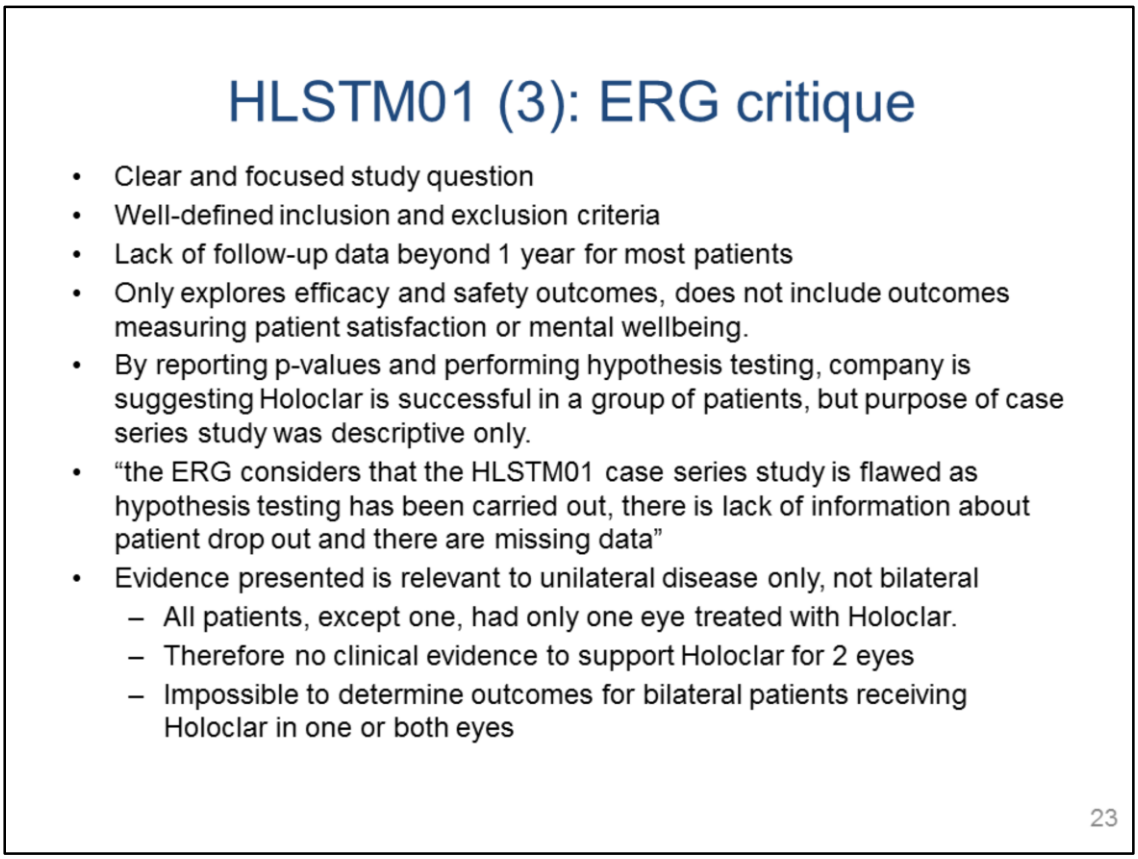
Visual acuity measured using the Snellen chart.

The number of patients with symptoms of LSCD (pain, blurring, and photophobia) decreased between baseline and 12 months post-surgery.

# HLSTM01 (2): adverse events

- 6 serious adverse events (3 fatal) after 6 transplantation procedures (representing 5.3% of total patients) all in patients who had had one transplant (none treatment-related).
- 22 adverse drug reactions (16.8%) after 19 transplantations.
- One case of gastritis and 5 of glaucoma that were possibly related to treatment with corticosteroids.
  - One case of glaucoma was considered to be treatment-related.

21




The company made the assumption that bilateral transplantation has the same success rate as unilateral transplantation, because there was no clinical evidence to support using Holoclar bilaterally. ERG stated this is unlikely to be the case because:

- Holoclar requires a biopsy of 1-2mm$^2$ of undamaged limbus for biopsy. In the bilateral case this has to be taken from a damaged eye. The company assumes that there is no difference in patient outcomes whether the limbal cells are taken from a damaged or undamaged eye. However in unilateral the biopsy is performed on the healthy eye and not on the eye that is already damaged (but has some healthy limbus). This suggests that there must be a clinical reason underlying the decision to take a biopsy from the healthy eye rather than from the damaged eye; whether this rationale is related to improved efficacy and patient outcomes is not known. The ERG speculated that it may be more difficult to locate and extract healthy limbal cells from a damaged eye than from a healthy eye.
- The company assumed that the same number of biopsies can be taken from a healthy eye as from a damaged eye. Whether using a damaged or undamaged eye, the company states that there is a 10% chance that the first biopsy will fail. The company also states that the Holoclar transplant itself can be carried out up to three times even if the first and second transplants fail. This means that a total of six biopsies could be required from a damaged eye that may only have 1-2mm$^2$ of undamaged limbus. The ERG did not consider this to be plausible. By default, that means that, even if the success rate per transplant is the same, overall efficacy of bilateral transplantation will be lower than the efficacy of unilateral transplantation simply due to the lower number of transplants that could be performed in patients undergoing bilateral intervention.

The company also states that multiple grafts can be grown from a single biopsy and that these can be

frozen and used should the initial graft fail. This would potentially allow for only a single biopsy to be taken from a damaged eye and be used bilaterally if required. However, the company presents no evidence on the success rates with frozen and defrosted grafts nor does it indicate what the costs of this option would be. As such, the ERG stated this approach should not be considered in the company submission, and the company had rightly not included it as an option in the economic model.

Given the clinical reasons to doubt the equal efficacy of using Holoclar unilaterally and bilaterally, and the absence of supportive clinical effectiveness evidence available, the ERG considered the assumption of equal efficacy to be unfounded.

# HLSTM02 and HLSTM04: study results

- **HLSTM02** (n=29), 12 month follow up
  - Primary outcomes: total 46 adverse events (AEs) in 19 patients (65.5%). 5 serious adverse events (SAEs) in 3 patients (10.3%) ; 3 SAEs in 2 patients were treatment-related
  - Secondary outcomes: **success** reported in 19 patients (65.5%; 95% CI: 48.2 to 82.8%); **failure** reported for 6 patients (20.7%) and information missing for 4 patients (13.8%).
- **HLSTM04** (n=15)
  - **success** reported in 9 patients (60%) at 90 day follow-up and maintained until final visit [mean 217 days (85 to 777 days)]
  - Improvements in VA at both day 90 and last visit despite majority of study population showing stromal scarring.
  - difficult to assess data on presence of clinical symptoms due to missing data at the baseline (60%).

24

# HLSTM02 and HLSTM04: ERG critique

- **HLSTM02** (n=29)
  - study question not detailed,
  - length of patient enrolment period not stated
  - lack of information about patient drop outs
  - only efficacy and safety outcomes but no outcomes measuring patient satisfaction or mental well-being
  - only descriptive statistics and no attempts to make absolute conclusions
- **HLSTM04** (n=15)
  - subjective outcomes not assessed by independent blinded assessor so could have been influenced by the investigators
  - high levels of missing data present with no reasons provided on why they are missing.
  - study only included efficacy and safety outcomes without measuring patient satisfaction or mental well-being

25

# Comparator outcomes: Ocular stability

**CLAU**

- 11 studies found, 5 studies exclusively in patients with ocular burns, and 4 reported success. All unilateral. Rates in 4 studies were:
  - 14/16 (**87.5%**) (or 14/21 (**66.7%**) with cases requiring a second transplantation taken into account);
  - 5/6 (**83.3%**)
  - 15/16 (**94%**)
  - 6/6 (**100%**).

**CLAL/KLAL**

- 11 studies found, 4 studies exclusively in patients with ocular burns (2 unilateral and 2 bilateral), and 3 reported success. Rates in 3 studies were:
  - 4/5 (**80%**),
  - 20/20 (**100%**)
  - 6/10 (**60%**).
- In addition, in study not exclusively on ocular burns, success was seen in 41% of the ocular burns patients.

26

# Comparator outcomes: Visual acuity

**CLAU**

- 11 studies found; 5 studies were conducted exclusively in patients with ocular burns. 4 studies reported visual acuity improvement:
  - 6/6 (**100%**),
  - 9/13 (**69%**),
  - 1/5 (**20%**),
  - 10/10 (**100%**)

**CLAL/KLAL**

- 15 studies identified; 4 studies were conducted exclusively in patients with ocular burns. 3 studies reported visual acuity improvement:
  - 13/20 (**65%**),
  - 8/10 (**80%**)
  - 17/17 (**100%**)
- The ERG noted that 1 study was conducted in patients with unilateral LSCD, 1 study was conducted in patients with bilateral LSCD and 1 study was conducted in a mixed patient group.

27

## Comparator: Adverse events

| | CLAU | KLAL/CLAL |
|---|---|---|
| Engraftment failure* | 10% (half of cases will cause persistent epithelial defect) | 20% (half of cases will cause persistent epithelial defect) |
| Infection | 20% of grafted eyes<br>5% of the donor eyes | 20% of grafted eyes<br>5% of the donor eyes (Lr-CLAL) |
| Glaucoma | 5-10% of patients | 10% of patients |
| Treatment failure (with recurrence of LSCD) | 20-30% of patients within 10 years | All treatments will fail within 3-5 years |
| * Based on clinical advice to the company | | |

28

Data were not available from studies reporting treatment with **BSC**.

- Clinical advice to company is that patients are likely to experience inflammatory flare-ups and treatment failures that result in epithelial defects.
- Approximately 90% of patients experience one flare-up and 50% of patients experience two flare-ups annually. There are also patients who experience three flare-ups each year.
- Approximately 5% of patients experience microbial keratitis once each year and 10% to 20% of patients need hospital treatment for infection or persistent epithelial defect each year.
- Infection and persistent epithelial defect are treated in hospital for between 5 and 7 days (but length of stay can be up to 14 days).
- Glaucoma resulting from steroid treatment is reported in 10% of patients who are treated chronically with steroids.

# Comparator studies: ERG critique

- Studies largely retrospective, observational and small numbers of patients
- Both company and ERG agree that:
  - comparator study results should be viewed with caution because of heterogeneous populations and interventions, and weak study design.
  - any pooling of data from the comparator studies is inappropriate.

29

# Comments from clinical experts

- A major step forward for patients because of:
  - higher success rate due to the confirmed presence of a sufficient proportion of stem cells prior to graft release.
  - ability to repeat the procedure without undue risk to the patients fellow eye from which the biopsy is taken.
- Trial population reflects NHS population
- Serious side effects or adverse reactions extremely rare and are usually associated with the eye surgery itself rather than the technology

30

## Cost-effectiveness evidence

- Company included 1 published study which modelled Holoclar transplant (used data from HLSTM01)
- 30 year extrapolation of visual acuity gain linked to utility. 3% discount rate
- Visual acuity, pain, burning and photophobia used to assess QoL and QALYs.
- Interventions:
  - Holoclar: QALYs: 15.93 to 22.49; total utility gain: 5.25 to 6.04 QALYs
  - Conservative treatment: QALYs: 10.29 to 17.24 (depending on severity of LSCD)
- Holoclar remains cost-effective (at maximum acceptable ICER of £30,000 per QALY gained) up to treatment cost of £150,000
- Company: not clear whether best or worst seeing eye utility is used; utility decrements for pain, photophobia and burning have no referenced source; no sensitivity analysis for time-invariant effectiveness over 30-year period despite evidence source duration being just 1 year.
- ERG: reservations about quality, unclear if methodology is robust. Given issues highlighted by company, ERG does not place any weight on results

Source: CS, p. 179 31

All results were discounted at 3% discount rate.

The model itself is an extrapolation of 1-year visual acuity gain linked to utility and extrapolated over a further 30 year period.

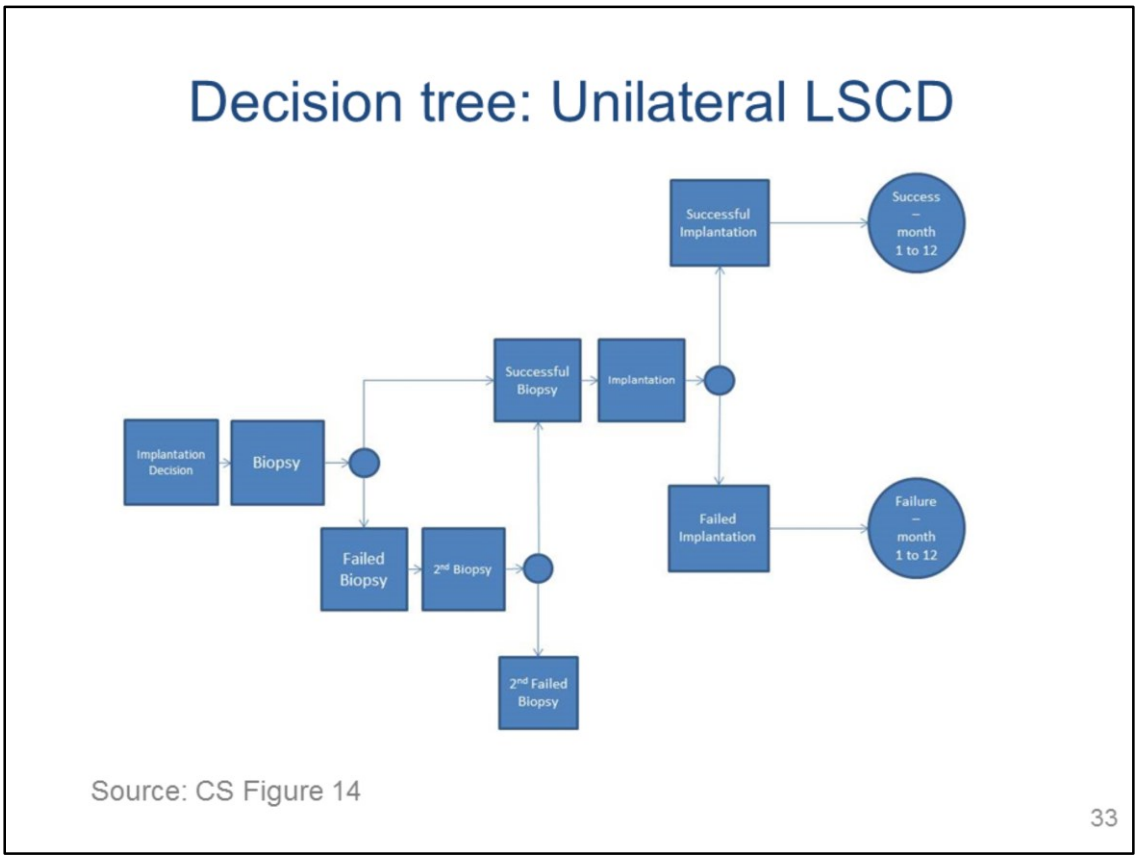
## Company model

- 2 base cases, unilateral and bilateral
- Population: males only; mean age: 46; visual acuity score: 10
- Holoclar compared with:
  - conjunctival-limbal autograft (CLAU)
  - limbal epithelial stem cells allografts:
    - living-related conjunctival allograft (Lr-CLAL)
    - keratolimbal allogeneic transplantation (KLAL)
  - Best supportive care (BSC).
- Company assumes some patients with stromal scarring receive keratoplasty 1 year after a successful Holoclar transplantation.
- Time horizon: lifetime (50 years)
- Discount rate: 1.5% (company stated this was because Holoclar has prolonged effect and can return patients to a high utility state)
- Model consists of decision tree (initial treatment phase with biopsy and treatment success or failure and retreatment if needed) followed by annual-cycle Markov model for longer term outcomes
- Company note that "regenerative technology for an ultra-orphan condition" makes modelling extremely challenging and standard reference case model possibly not appropriate

32

Each model consists of a decision tree - initial treatment phase which permits biopsy and transplant success and failure and re-transplant where appropriate followed by a yearly Markov structure which permits states stable state; failed BSC state and death. At year one keratoplasty surgery is incorporated for a proportion of patients with stromal scarring and successful transplant.

Best supportive care is defined as topical steroids, ocular lubricants, bandage contact lenses and autologous serum eye drops.




Decision tree:

Patients have biopsy which can be success or fail

If successful they progress to Holoclar implant

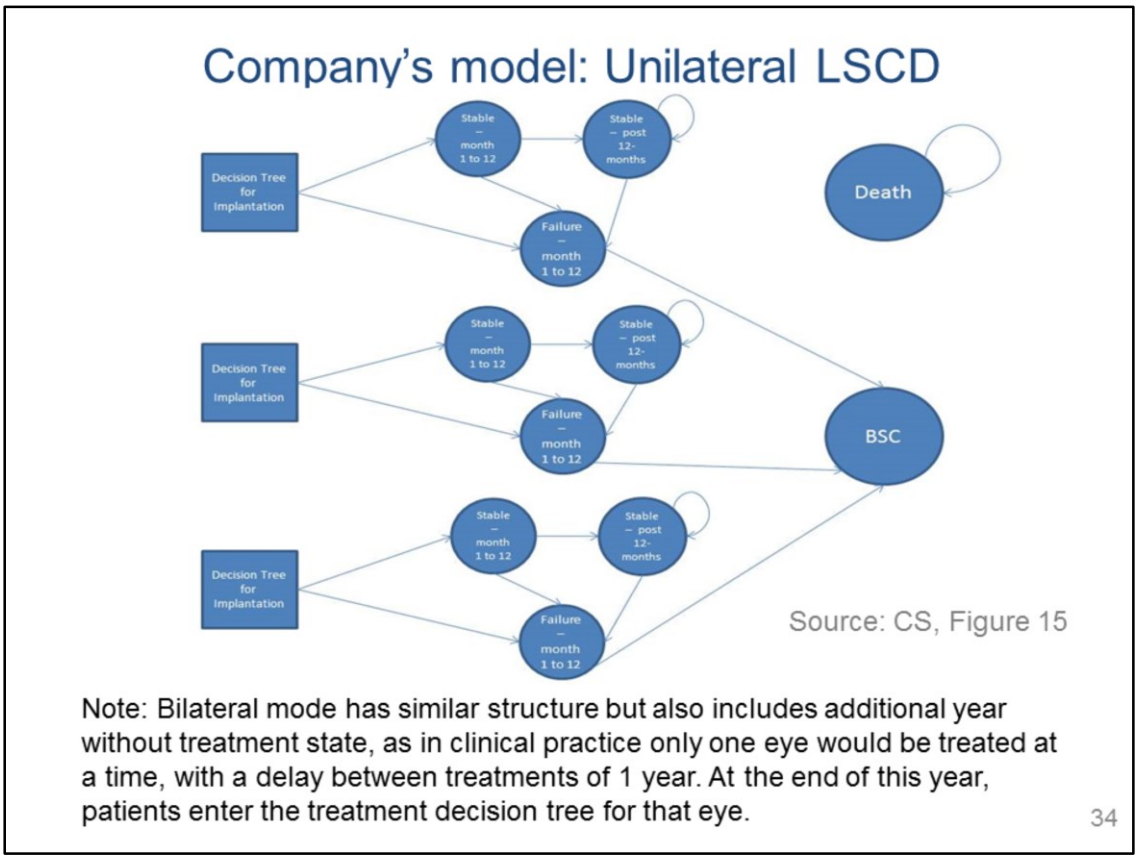
If fail they undergo 2nd biopsy (again also success or fail; if unsuccessful move to 'Failure' state in Markov model).

Holoclar impact can be success or fail

If success patients enter Markov model in 'Stable Month 1 to 12' state

If fail patients enter Markov model in 'Failure' state

- Each biopsy associated with cost and QALY decrement.




Patients enter Markov model in either the 'Stable months 1 to 12' state or the 'Failure' state (dependent on the prior decision tree)

Those 'Stable months 1 to 12' either remain in that state or implant may fail and then would to 'Failure'.

For those who remain stable and progress to the Stable post 12 months state, some will be eligible for a keratoplasty at 12 months.

Patients who enter the Stable post 12 months state will continue in this state or, at some point in the future, their HOLOCLAR implantation may fail, and move to 'Failure'.

Patients in 'Failure' state remain there for 1 year, at which point they either re-enter decision tree for 2nd HOLOCLAR treatment, or move to 'BSC'.

Patients can undergo a maximum of 3 Holoclar treatments

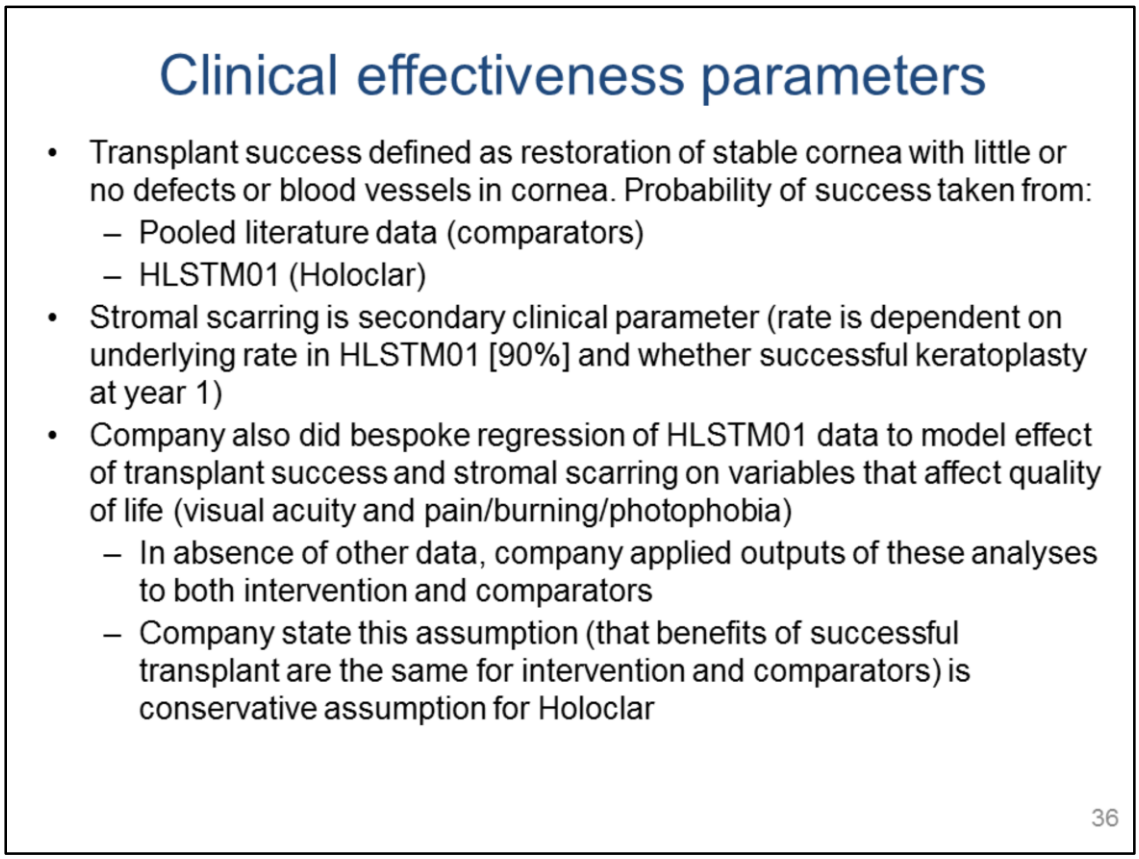
Patients in all states may die.

The same model structure has been used for the intervention and comparators, except for patients receiving CLAU, no biopsy procedure is required.

# ERG critique: Model structure

- For CLAU and Holoclar company assume patients with successful transplants at 12 months have successful transplants for life. However:
  - No evidence to support this
  - Cannot be modified – inherent model weakness
- Company discount rate 1.5% (NICE reference case is 3.5%)
  - NICE can accept 1.5% if treatment restores people who would otherwise die or have severely impaired life, to full or near full health, sustained over very long period (normally >30 years)
  - Holoclar does not meet these conditions – does not extend life, and extent of impact of LSCD on QoL, and extent to which Holoclar can affect this impact, is unknown
  - ERG used 3.5% in exploratory analyses

35




The presence of stromal scarring is dependent upon the underlying rate within the presenting patient populations (determined as 90% from HLSTM01) and whether a successful keratoplasty has been conducted (at year one). This is conditional on stromal scarring being present within an individual and the presence of a successful transplant at year one. However even then not all patients will undergo a keratoplasty with this conditional probability being estimated as 57% from HLSTM01. A success rate of 98% is used for Keratoplasty success, which again is derived from the HLSTM01 data.

## Relationship between transplant success, stromal scarring and **visual acuity**

- Random effects ordered logistic regression model
- Visual acuity (dependent variable) generated by converting to 13-point scale, from light perception to 10/10 best corrected visual acuity.
- Company assume relationship between visual acuity and transplant success is same as observed in the HLSTM01 case series study at 12 months and remains constant over time.
- Company presented post-treatment visual acuity results for patients with 3 different baseline levels of visual acuity: good (top 25% of random effects model), poor (bottom 25%) and average
- Visual acuity probability was calculated for 6 groups of patients:
  - Baseline patients: with and without stromal scarring
  - Transplant failure: with and without stromal scarring
  - Transplant success: with and without stromal scarring

37

## Probability of VA states for the **average** affected eye

| Visual acuity | Baseline (%) | | Failure (%) | | Success (%) | |
|---|---|---|---|---|---|---|
| | with SS | w/o SS | with SS | w/o SS | with SS | w/o SS |
| Light perception (1) | 4.67 | 0.32 | 1.22 | 0.08 | 0.27 | 0.02 |
| Hand movement(2) | 46.32 | 5.99 | 19.58 | 1.59 | 5.21 | 0.36 |
| Finger count (3) | 44.41 | 50.97 | 63.14 | 23.62 | 48.11 | 6.58 |
| 1 (4) | 2.41 | 17.00 | 7.90 | 16.87 | 17.73 | 6.91 |
| 2 (5) | 1.17 | 12.00 | 4.24 | 19.18 | 13.09 | 12.09 |
| 3 (6) | 0.48 | 6.02 | 1.82 | 13.81 | 6.76 | 14.10 |
| 4 (7) | 0.32 | 4.48 | 1.25 | 13.17 | 5.11 | 22.52 |
| 5 (8) | 0.11 | 1.61 | 0.43 | 5.54 | 1.85 | 14.62 |
| 6 (9) | 0.05 | 0.76 | 0.20 | 2.81 | 0.88 | 9.35 |
| 7 (10) | 0.03 | 0.43 | 0.11 | 1.64 | 0.50 | 6.29 |
| 8 (11) | 0.02 | 0.35 | 0.09 | 1.37 | 0.41 | 5.79 |
| 9 (12) | 0.00 | 0.06 | 0.02 | 0.24 | 0.07 | 1.07 |
| 10 (13) | 0.00 | 0.02 | 0.00 | 0.07 | 0.02 | 0.30 |
| Key: SS - stromal scarring, w/o – without | | | | | | |

Source: CS table 23

38

## Probability of VA states for **good** underlying VA

| Visual acuity | Baseline (%) | | Failure (%) | | Success (%) | |
|---|---|---|---|---|---|---|
| | with SS | w/o SS | with SS | w/o SS | with SS | w/o SS |
| Light perception | 0.49 | 0.03 | 0.12 | 0.01 | 0.03 | 0.00 |
| Hand movement | 8.96 | 0.64 | 2.44 | 0.16 | 0.55 | 0.04 |
| Finger count | 58.05 | 11.18 | 31.83 | 3.11 | 9.80 | 0.71 |
| 1 | 14.23 | 10.60 | 18.64 | 3.53 | 9.58 | 0.84 |
| 2 | 8.96 | 16.21 | 18.05 | 6.92 | 15.23 | 1.81 |
| 3 | 4.20 | 15.92 | 11.33 | 9.55 | 15.67 | 2.88 |
| 4 | 3.01 | 20.47 | 9.73 | 19.88 | 21.29 | 8.08 |
| 5 | 1.06 | 10.85 | 3.81 | 17.43 | 11.84 | 10.98 |
| 6 | 0.50 | 6.16 | 1.87 | 13.92 | 6.90 | 13.88 |
| 7 | 0.28 | 3.84 | 1.08 | 10.99 | 4.38 | 17.33 |
| 8 | 0.23 | 3.35 | 0.89 | 11.55 | 3.85 | 31.34 |
| 9 | 0.04 | 0.60 | 0.15 | 2.30 | 0.69 | 9.24 |
| 10 | 0.01 | 0.16 | 0.04 | 0.65 | 0.19 | 2.87 |
| Key: SS – stromal scarring, w/o - without | | | | | | |

Source: CS table 24

39

## Probability of VA states for **poor** underlying VA

| Visual acuity | Baseline (%) | | Failure (%) | | Success (%) | |
|---|---|---|---|---|---|---|
| | with SS | w/o SS | with SS | w/o SS | with SS | w/o SS |
| Light perception | 32.81 | 3.06 | 10.98 | 0.79 | 2.65 | 0.18 |
| Hand movement | 58.40 | 37.11 | 61.40 | 13.71 | 34.00 | 3.43 |
| Finger count | 8.31 | 52.86 | 25.74 | 62.65 | 55.36 | 39.11 |
| 1 | 0.26 | 3.60 | 1.00 | 10.76 | 4.11 | 18.91 |
| 2 | 0.12 | 1.79 | 0.48 | 6.15 | 2.06 | 16.13 |
| 3 | 0.05 | 0.74 | 0.19 | 2.73 | 0.86 | 9.20 |
| 4 | 0.03 | 0.50 | 0.13 | 1.90 | 0.58 | 7.39 |
| 5 | 0.01 | 0.17 | 0.04 | 0.66 | 0.20 | 2.78 |
| 6 | 0.01 | 0.08 | 0.02 | 0.31 | 0.09 | 1.34 |
| 7 | 0.00 | 0.04 | 0.01 | 0.17 | 0.05 | 0.77 |
| 8 | 0.00 | 0.04 | 0.01 | 0.14 | 0.04 | 0.63 |
| 9 | 0.00 | 0.01 | 0.00 | 0.02 | 0.01 | 0.11 |
| 10 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.03 |
| Key: SS – stromal scarring, w/o - without | | | | | | |

Source: CS table 25

40

## Relationship between transplant success, stromal scarring and **pain, burning, photophobia**

- Company combined data for outcomes pain/burning/photophobia into 'any' category (used as dependent variable) using highest result overall for each patient
- Company only presented results for average patient because there was less heterogeneity than for visual acuity outcome

**Table: Predicted probabilities of pain/burning/photophobia**

| | Baseline (%) | | Failure (%) | | Success (%) | |
|---|---|---|---|---|---|---|
| | with SS | w/o SS | with SS | w/o SS | with SS | w/o SS |
| None | 57.5 | 79.3 | 77.6 | 90.8 | 88.6 | 95.7 |
| Mild | 28.5 | 15.3 | 16.4 | 7.1 | 8.6 | 3.4 |
| Moderate | 13.5 | 5.3 | 5.8 | 2.1 | 2.7 | 0.96 |
| Severe | 0.56 | 0.2 | 0.2 | 0.08 | 0.1 | 0.03 |

SS - stromal scarring; w/o - without

Source: CS table 30

41

# Relationship between transplant success, keratoplasties and stromal scarring

- HLSTM01 included dates and outcomes of additional surgery (including keratoplasty), and eye examinations contained data on stromal scarring.
- This provided indirect link (via probability of stromal scarring) between keratoplasty and its impact on visual acuity.
- The probability of stromal scarring at different points in the pathway estimated from random effects logistic regression
- Results show that only keratoplasty has any significant impact on the probability of stromal scarring.

| | Baseline | Failed transplant | Successful transplant | Successful transplant plus successful keratoplasty |
|---|---|---|---|---|
| No stromal scarring | 9.62% | 11.08% | 11.46% | 81.58% |
| Stromal scarring | 90.38% | 88.92% | 88.54% | 18.42% |

Source: CS Table 34

42

# ERG critique clinical effectiveness

- Absence of clinical effectiveness data to support Holoclar to treat both eyes
- Issues with data quality noted in clinical effectiveness section – these flaws equally apply in model
- Company stated in clinical section it was inappropriate to pool clinical data because of parameter heterogeneity, yet it uses pooled data in the model
  - As individual studies have very small sample sizes, doubtful that selection of any study will produce more robust results than pooled analysis.
  - But weak evidence for comparators needs to be taken into account when assessing robustness of ICERs

43

# Health-related quality of life (HRQoL)

- No studies reporting utility scores relating to LSCD
- Company took 2 broad approaches to derived modelled utility values:
  1. bespoke standard gamble (SG) stated preference exercise (520 members of public)
  2. burden of disease systematic review identified key symptoms that drive overall utility of patients with LSCD: visual acuity, pain, burning, photophobia and disfigurement. Company did additional literature search for associated disutility values
- Pain is a probabilistic function of health states
- Disfigurement assumed to be present in all states except for those patients in stable condition with no stromal scarring.

44

## Health-related quality of life (1)

| State | VA based utility | Pain/burning /photophobia | Disfigurement | **Overall utility** |
|---|---|---|---|---|
| Baseline with stromal scarring | 0.56 | -0.019 | -0.318 | **0.223** |
| Baseline without stromal scarring | 0.60 | -0.007 | -0.318 | **0.275** |
| Transplant failure/ BSC with stromal scarring | 0.57 | -0.008 | -0.318 | **0.244** |
| Transplant failure/ BSC without stromal scarring | 0.63 | -0.003 | -0.318 | **0.309** |
| Transplant success – stable with stromal scarring | 0.60 | -0.004 | -0.318 | **0.278** |
| Transplant success – stable without stromal scarring | 0.67 | -0.001 | - | **0.669** |
| Death | 0 | - | - | **0** |

Source: CS Table 48

45

In both models, utility is driven by the combination of VA in both the best seeing eye (BSE) and worst seeing eye (WSE). The utility value assigned to any combination is a function of the underlying BSE based utility mappings applied to an algorithm which splits the mapping from a single VA measurement to a BSE/WSE combination to utility mapping. Company stated it used Czoski-Murray et al group means original mapping because it has an established use in NICE HTA algorithms and applies a weighting estimated from Finger et al data.

An additional utility decrement can occur if there is moderate or severe pain/burning/photophobia. The company stated these secondary conditions were modelled together because there was a high degree of correlation between them in the HLSTM01 dataset. The base case value attached to the presence of moderate or severe pain/burning/ photophobia is derived from the EQ-5D 3L tariff and uses the level 2 and 3 decrements of -0.123 and -0.386 respectively. Alternative values of no decrement and that derived from the general population SG method of -0.291 for both moderate and severe may be used.

A final utility decrement can occur due to disfigurement which as defined as the presence of either/or corneal opacity, superficial corneal neovascularisation and inflammation. In practice this is measured as an eye with an unsuccessful transplant or the presence of stromal scarring. If there is disfigurement in any eye, then the base case utility decrement from the general population SG is used and a value of -0.318 is used. As with pain, an alternative of zero utility decrement can be selected.

# ERG critique: HRQoL

- No HRQoL data available for Holoclar or comparators – therefore absolute and comparative HRQoL benefits of Holoclar are unknown
- Company made "laudable attempt" to estimate values given there are none available, however values used are implausibly low
  - E.g. most utility values are <0.36; however this is lower than for palliative cancer treatment in last 3 months of life; also lower than other eye-related appraisals
- More appropriate utility values should be chosen – 2 factors that drive the low values and, for each of these factors, alternatives can be used.
  - Company choice of VA utility values. ERG used alternative source with more plausible value 0.840 instead of max 0.706
  - Company 0.318 decrement for disfigurement in any eye to all who do not have successful keratoplasty, applied equally regardless of extent of disfigurement. ERG used alternative source with more plausible value (0.140 decrement)
- ERG used these alternative utility values in its exploratory analyses

46

# Adverse events

- Company stated inconsistent and incomplete description of adverse events in studies meant that it instead used expert clinical opinion, and Holoclar statement of product characteristics
- Glaucoma is only adverse event described in submission
- Not associated with QALY decrement (based on literature) but involves cost

| Procedure | Rate | Source |
|---|---|---|
| CLAU | 5% | Expert opinion |
| Lr-CLAL | 10% | |
| KLAL | 10% | |
| Holoclar | 3.5% | SmPC |

Source: CS p. 221

47

## Resources and costs - extraction biopsy

| Resource item | Cost | Treatment | Number |
|---|---|---|---|
| Minor eye procedure | £675.73 | Holoclar | 1 |
| | | CLAU | 0 |
| | | Lr-CLAL | 1 |
| | | KLAL | 0 |
| Amniotic membrane | £[redacted] | Holoclar | 0 |
| | | CLAU | 1 |
| | | Lr-CLAL | 1 |
| | | KLAL | 2 |
| Bandage contact lens applied by an ophthalmologist | £4.17 | CLAU only | 1 |
| Outpatient appointment | £60.13 | Holoclar | 1 |
| | | CLAU | 0 |
| | | Lr-CLAL | 5 |
| | | KLAL | 0 |
| Antibiotic eye drops | £0.007 | All | 4 x day, 3 weeks |
| Steroid eye drops | £0.01 | All | 4 x day, 3 weeks |
| Artificial tears | £0.037 | All | 4 x day, 3 weeks |

Source: CS table 49

48

Source of information provided in the company submission and ERG report.

Company presented procedural resource use and costs in two sections for those relating to: the initial biopsy (this slide), and main transplant (next slide). ERG noted it identified some minor discrepancies between values used in submission and values used in models.

## Resources and costs - main transplant

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| Holoclar | [redacted] | Intervention-specific costs | 1 | Company submission |
| CLAU | £0 | | 1 | |
| Ir-CLAL | £0 | | 1 | |
| KLAL | £[redacted] | | 1 | Single Cornea- NHS Blood and Transplant |
| Surgery | £2,934 | All | | NHS Reference Cost: Very Complex, Cornea or Sclera Procedures with CC Score 0-1 |
| Amniotic membrane | £[redacted] | Holoclar | 0 | Frozen amniotic membrane 2x2cm<br>NHS Blood and Transport |
| | | CLAU | 1 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 2 | |

Source: CS table 49

49

# Health state costs (1)

| Resource item | Cost | Treatment | Number |
|---|---|---|---|
| **Stable first 12 months** | | | |
| Antibiotic eye drops | £0.01 | Holoclar | 0 |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months |
| Steroid eye drops | £0.01 | Holoclar | 0 |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months |
| Artificial tears | £0.04 | Holoclar | 0 |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months |
| Autologous serum eye drops | £[redacted] | Holoclar | 0 |
| | | CLAU, Lr-CLAL, KLAL | 2 |
| Outpatient appointments* | £60 | Holoclar | 5 |
| | | CLAU, Lr-CLAL, KLAL | 10 |
| Immunosuppressants (costs not included within the models) | | For 12 months for patients who received Lr-CLAL or KLAL | |
| **Stable post-12-months:** No on-going treatment required | | | |
| **Failure**: No cost associated with failure (1st 12 months post-transplant failure allocated same resource use as BSC) | | | |

*weekly <2months, fortnightly 3– 6 months, monthly 6-12 months (22 appointments) 50

# Health state costs (2)

| Resource item | Cost | Treatment | Number |
|---|---|---|---|
| **Best supportive care** | | | |
| Regular ophthalmology outpatient appointments | £60 | All | 6 per year |
| Antibiotic eye drops | £0.01 | All | 4 x day |
| Steroid eye drops | £0.01 | All | 4 x day |
| Artificial tears | £0.04 | All | 4 x day |
| Flare-ups | | Treated with autologous serum eye drops and a course of oral antibiotics | 2 x year |
| Autologous eye drops | £[redacted] | | |
| Oral antibiotics | £0.09 | | |
| **Keratoplasty** | | | |
| Keratoplasty product | £[redacted] | All | |
| Major eye procedure | £[redacted] | All | |
| Outpatient appointments | £60 | All | 6 |
| Antibiotic eye drops | £0.01 | All | 4 x day, 2 months |
| Steroid eye drops | £0.01 | All | 4 x day, 2 months |
| Artificial tears | £0.04 | All | 4 x day, 2 months |

51

## ERG critique: resources and costs

- Clinical advice to ERG: several costs not relevant to any procedure (however impact of these small and not discussed further)
- 2 key areas have significant impact on incremental costs:
  1. Post op autologous serum eye drops: used for comparators but for Holoclar only used <3 months. But unlikely that surgeon currently using them for CLAU, Lr-CLAL or KLAL will not use them for Holoclar
  2. Use of autologous serum eye drops for flare-up: varied clinical practice and biggest driver of costs in company model therefore should have 2 scenarios (treatment with and without the use of autologous serum drops for flare-ups)

52

Adding or removing a cost of use of the autologous serum eye drops that is the same for all procedures makes no difference to the size of the incremental costs estimated between procedures; adding the cost of post-operative autologous serum eye drops to Holoclar or removing the cost from the alternative procedures has equal effect on the size of the ICER per QALY gained. The ERG has therefore added the cost to Holoclar.

# Company base case without PAS

| Unilateral | Incr. costs | Incr. QALYs | ICER vs BSC | ICER w/o CLAU |
|---|---|---|---|---|
| CLAU | | | Dominates | |
| Lr-CLAL | £[redacted] | -2.92 | Dominates | |
| KLAL | £[redacted] | 0.07 | Dominates | Extendedly Dominated |
| BSC | £[redacted] | -2.62 | - | Dominated |
| Holoclar | £[redacted] | 4.91 | £[redacted] | £[redacted] |
| Bilateral LSCD | | | | |
| CLAU | | | Dominates | - |
| Lr-CLAL | [redacted] | -3.72 | Dominates | |
| KLAL | [redacted] | 0.20 | Dominates | Extendedly Dominated |
| BSC | [redacted] | -4.12 | - | Dominated |
| Holoclar | [redacted] | 6.81 | £[redacted] | £[redacted] |

**Note: All treatments dominated by CLAU**

Source: CS appendix 9, tables 1 and 8

53

# Company base case with PAS

- In both unilateral and bilateral models, all treatments dominated by CLAU
- For bilateral, company and ERG agree CLAU is not plausible procedure

| Unilateral pairwise, Holoclar vs comparator | | | |
|---|---|---|---|
| | Incr. costs | Incr. QALYs | ICER |
| Holoclar | - | - | - |
| CLAU | -£72,264 | 0.55 | Holoclar dominated by CLAU |
| Lr-CLAL | -£16,988 | -2.36 | £7,185 |
| KLAL | - £5,167 | -2.29 | £2,255 |
| BSC | £7,112 | -4.91 | Holoclar dominates BSC |

| Bilateral pairwise, Holoclar vs comparator | | | |
|---|---|---|---|
| Holoclar | - | - | - |
| CLAU | -£144,014 | 0.83 | Holoclar dominated by CLAU |
| Lr-CLAL | -£35,986 | -2.89 | £12,438 |
| KLAL | - £17,572 | -2.69 | £6,533 |
| BSC | £1,906 | -6.81 | Holoclar dominates BSC |

Source: ERG tables 25, 27

54

## Company sensitivity analyses

| Scenario | ICER per QALY gained | | | |
|---|---|---|---|---|
| | CLAU | Lr-CLAL | KLAL | BSC |
| **Unilateral deterministic sensitivity analyses** | | | | |
| Base case | Dominated | £7,185 | £2,255 | Dominant |
| 1. 3.5% discount rates | Dominated | £21,182 | £15,245 | £3,563 |
| 2. No disfigurement utility decrement | Dominated | £35,076 | £11,546 | Dominant |
| 3. 1+2+ 4 flares per year BSC | Dominated | £25,164 | £7,586 | Dominant |
| 4. 2+ alternative comp. success rates | £488,615 | £487 | £9,138 | Dominant |
| 5. Alternative rates+time horizon 22yr | £167,201 | £13,651 | £29,488 | £5,743 |
| **Bilateral deterministic sensitivity analyses** | | | | |
| Base case | Dominant | £12,438 | £6,533 | Dominated |
| 1. 3.5% discount rates | Dominant | £34,817 | £29,818 | £6,708 |
| 2. No disfigurement utility decrement | Dominant | £31,850 | £21,861 | Dominated |
| 3. 1+2+ 4 flares per year BSC | Dominant | £26,384 | £39,595 | Dominated |
| 4. 2+ alternative comp. success rates | £486,145 | £1,928 | £19,049 | Dominated |
| 5. Alternative rates+time horizon 22yr | £255,563 | £11,368 | £27,898 | £5,060 |

**Probabilistic sensitivity analyses**: 100% likelihood of CLAU being most cost effective

Source: CS tables 58, 60, 62, 64, 66

55

The company presents a number of scenario analyses based on changes to some key assumptions in the models. The parameters varied include the discount rate, the utility value for disfigurement, the success of comparative surgical interventions and the timeframe over which cost effectiveness is assessed in the models.

# ERG critique: company results

Several fundamental issues that cast doubt on results:

- All treatments are more expensive/less effective than CLAU
- Weak clinical evidence base for all treatments; case series yield low quality evidence and company pool comparator data despite stating inappropriate
- Bilateral results "extremely limited… to the point of being non-informative"
  - Effectiveness evidence limited to 1 patient.
  - Plausible clinical reasons why Holoclar may not be as effective when used to treat bilateral vs unilateral LSCD
- Utility values implausible
- Discount rate should be 3.5%, not 1.5%
- Doubt about where in pathway autologous serum eye drops are used. Model sensitive to this, eye drops account for substantial proportion of BSC costs
- Implausible that no 2nd procedure for unilateral LSCD after Lr-CLAL failure
- Models do not include failure rates >12 months after successful transplant.

56

## ERG exploratory analysis - Unilateral

| Scenario for Holoclar vs treatment | vs Lr-CLAL | vs KLAL | vs BSC |
|---|---|---|---|
| **A. Company base case** | **£7,185** | **£2,255** | **Dominates** |
| 1. Use of Brown 2003 VA utility values | £7,576 | £2,367 | Dominates |
| 2. ERG preferred decrement for disfigurement | £12,960 | £4,107 | Dominates |
| **B. ERG preferred utility scenario (1+2)** | **£14,291** | **£4,494** | **Dominates** |
| 3. 3.5% discount rate | £21,182 | £15,245 | £3,563 |
| **C. ERG preferred utility +3.5% discount (1-3)** | **£42,139** | **£30,415** | **£6,948** |
| 4. Holoclar post-op autologous serum eye drops | £8,129 | £3,239 | Dominates |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (1-4)** | **£45,048** | **£33,473** | **£8,155** |
| 5. Eye drops not used flare-ups | £23,328 | £16,766 | £12,467 |
| **E. ERG utility, 3.5% discount, post-op eye drops+no use eye drops for flare-ups (1-5)** | **£76,963** | **£60,996** | **£35,489** |
| 6. Two attempts at Lr-CLAL | £30,415 | - | - |
| **F. All changes from ERG but continued use of eye drops for flare-up (1-4, 6)** | **£152,590** | - | - |
| **G. All suggested changes from ERG (1-6)** | **£179,066** | - | - |

**Note: Holoclar dominated by CLAU in all scenarios**

Source: ERG tables 34, 35, 36

57

# ERG exploratory analysis - Bilateral

| Scenario for Holoclar vs treatment | vs Lr-CLAL | vs KLAL | vs BSC |
|---|---|---|---|
| **A. Company base case** | **£12,438** | **£6,533** | **Dominates** |
| 1. Use of Brown 2003 VA utility values | £13,916 | £7,512 | Dominates |
| 2. ERG preferred decrement for disfigurement | £18,890 | £10,762 | Dominates |
| **B. ERG preferred utility scenario (1+2)** | **£22,524** | **£13,702** | **Dominates** |
| 3. 3.5% discount rate | £34,817 | £29,818 | £6,708 |
| **C. ERG preferred utility +3.5% discount (1-3)** | **£63,047** | **£69,455** | **£12,669** |
| 4. Holoclar post-op autologous serum eye drops | £13,923 | £8,130 | £351 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (1-4)** | **£67,219** | **£75,457** | **£14,288** |
| 5. Eye drops not used flare-ups | £37,138 | £28,237 | £18,980 |
| **E. ERG utility, 3.5% discount, post-op eye drops+no use eye drops for flare-ups (1-5)** | **£111,654** | **£122,468** | **£50,973** |

**Note: Scenarios vs CLAU not presented by ERG**

Source: ERG tables 37, 38, 39

58

# Innovation (1) Company

- Use of somatic stem cells from intended patient offers major advantages (vs embryonic stem cells) and allows for immediate therapeutic application.
- Holoclar offers several advantages over comparator technologies including lack of immunological rejection (avoids immunosuppression), smaller amount of donor tissue required, ability to treat both eyes and possibility of retreatment if needed. Holoclar may also offer a bridge to subsequent successful keratoplasty for some with LSCD complicated by deep stromal scarring, which can further improve VA
- Holoclar is the 1st stem-cell treatment and living cell-based treatment to receive European MA, and "the recommendation to approve Holoclar is considered one of the most significant milestones achieved by the EMA in the last 20 years"
- Meets unmet medical need for rare (estimated 121 patients per year eligible for Holoclar treatment) and debilitating orphan condition
- Holoclar won award for innovation and research – the UK Prix Galien Orphan Product award ("widely regarded as the highest distinction" for pharmaceutical product)
- Regenerative technology for ultra-orphan condition make modelling challenging and may standard reference case may not be appropriate

59

# Innovation (2) NICE policy regenerative medicine

- NICE and University of York investigated whether appraisal process was fit for purpose for regenerative medicine and cell therapy, recognising these technologies present special difficulties for appraisal because they can be (i) expensive per patient, (ii) be supported by a weak evidence base, but (iii) potentially confer substantial health gains.
- This was in response to recommendations from Department of Health Regenerative Medicine Expert Group (RMEG).
- NICE Regenerative Medicines and Cell Therapy report (2016) summarised:
  - NICE appraisal methods and decision framework are applicable to regenerative medicines and cell therapies.
  - Quantifying and presenting clinical outcome and decision uncertainty was key to Expert Panel consideration of hypothetical example products
  - Where combination of great uncertainty but potentially very substantial patient benefits, innovative payment methodologies needed to manage and share risk to help timely patient access while evidence immature
  - Discounting rate for costs/benefits had very significant impact

60

NICE Regenerative Medicines and Cell Therapy report available here:
https://www.nice.org.uk/Media/Default/About/what-we-do/Science%20policy%20and%20research/regenerative-medicine-study-march2016-2.pdf

Full report from University of York available here:
https://www.nice.org.uk/Media/Default/About/what-we-do/Science%20policy%20and%20research/final-york-report-march-16.pdf

# Equality considerations

- Company stated if Holoclar not made available a significant equality issue would arise for patients with LSCD due ocular burns that were incurred while serving in armed forces
- These patients likely to also have experienced loss of limbs or other life changing events or injuries, both physical and mental, over and above those experienced by the general population with same condition.

- ERG stated it does not consider this an equality or equity issue.

61

# Authors

- **Irina Voicechovskaja**
  Technical Lead
- **Carl Prescott**
  Technical Adviser
- with input from the Lead Team (Peter Selby, Judith Wardle, Paul Tappenden)

62

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns

## Final scope

### Remit/appraisal objective

To appraise the clinical and cost effectiveness of ex vivo expanded autologous human corneal epithelial cells containing stem cells within its marketing authorisation for treating moderate to severe limbal stem cell deficiency due to ocular burns.

### Background

The cornea is the clear, rigid layer covering the front of the eye and it is divided in 4 quadrants: superior, temporal, inferior and nasal. Cells on the cornea surface are constantly being renewed and replaced by limbal stem cells which are located in the ocular surface between the cornea and the bulbar conjunctiva. An injury to the source of the limbal stem cells can cause a deficiency of these cells known as limbal stem deficiency (LSCD), reducing the renewal and replacement of the surface of the cornea. This results in the cornea being repaired by different types of eye cell and excessive ingrowth of blood vessels (neovascularisation), which can make the cornea opaque and impair vision. Ocular burns because of chemicals or heat can damage these stem cells. Moderate to severe LSCD is defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity.

The estimated prevalence of LSCD due to ocular burns in Europe is 0.3 in 10,000 people[1], which is equivalent to about 1800 people in England. The number of corneal transplants for ocular surface burns is thought to be very small. It is estimated that approximately 90 to 100 people in England would be eligible for treatment with ex vivo expanded autologous human corneal epithelial cells containing stem cells[2].

The aim of current treatment is to restore a healthy conjunctival and corneal surface. Treatments include topical steroids, ocular lubricants, bandage contact lenses, autologous serum eye drops, oral and/or topical vitamin C and oral tetracycline. Historically, LSCD has been treated with surgical procedures based on tissue therapy. Tissue from the healthy eye has been used for conjunctival limbal autografts for people with unilateral LSCD, and tissue from a cadaver or a relative donor has been used for limbal epithelial stem cells allografts for bilateral disease. However these procedures are associated with a high risk of allograft rejection and damage to the healthy eye. There are no

specific treatments available for treating LSCD due to physical or chemical ocular burns.

## The technology

Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar, Chiesi Farmaceutici) is a treatment used in the eye to replace damaged cells on corneal surface. It consists of cells taken from the patient's limbus (at the edge of the cornea) and then grown in a laboratory and frozen until the date of surgery is confirmed. The cells are grown on a membrane made of a protein called fibrin and the final product is then sent back to the hospital, where it is immediately surgically implanted in the patient's eye.

Ex vivo expanded autologous human corneal epithelial cells containing stem cells has a conditional marketing authorisation in the UK for moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 $mm^2$ of undamaged limbus is required for biopsy. As part of the conditional marketing authorisation the company is conducting a prospective, open-label, uncontrolled interventional study to assess the efficacy and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns.

| | |
|---|---|
| **Intervention(s)** | Ex vivo expanded autologous human corneal epithelial cells containing stem cells |
| **Population(s)** | Adults with moderate to severe limbal stem cell deficiency (defined by th+e presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1 - 2 $mm^2$ of undamaged limbus |
| **Comparators** | For people with unilateral limbal stem cell deficiency:<br>• conjunctival limbal autograft<br>• best supportive care<br>For people with bilateral limbal stem cell deficiency:<br>• conjunctival limbal autograft<br>• limbal epithelial stem cells allografts<br>• best supportive care |

| | |
|---|---|
| **Outcomes** | The outcome measures to be considered include:<br>• clinical parameters of limbal stem cell deficiency including stability and transparency of the corneal epithelium and superficial corneal neovascularisation<br>• symptoms of limbal stem cell deficiency including pain, burning and photophobia<br>• visual acuity (the affected eye)<br>• visual acuity (the whole person)<br>• adverse effects of treatment<br>• health-related quality of life. |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.<br>The costs and effects of best supportive care when given in combination with the intervention should be taken into account. Best supportive care includes topical steroids, ocular lubricants, bandage contact lenses, autologous serum eye drops, oral and/or topical vitamin C and oral tetracycline. |
| **Related NICE recommendations and NICE Pathways** | Related Interventional Procedures:<br>'Corneal endothelial transplantation' (2009) NICE interventional procedures guidance 304<br>'Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium' (2007) NICE |

| | |
|---|---|
| | interventional procedures guidance 216<br>Related NICE Pathways:<br>Eye conditions (2015) NICE pathway.<br>http://pathways.nice.org.uk/pathways/eye-conditions |
| **Related National Policy** | Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 3, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf<br><br>NHS England (2014) Manual for prescribed specialised services 2013/14. Chapter 12. D12 - Adult specialist opthalmology services.<br><br>NHS England (2013) NHS standard contract for specialised ophthalmology (adult). Schedule 2 - the services - A. the specifications.<br><br>NHS England (2013) 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults). particulars, schedule 2- the services, a- service specification |

## References

1. European Medicines Agency (2015) Public summary of opinion on orphan designation. Accessed July 2015.

2. Company communication.

**Appendix C**

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency caused by burns to the eyes [ID899]

## Matrix of consultees and commentators

| Consultees | Commentators (no right to submit or appeal) |
|---|---|
| Company<br>• Chiesi Ltd (Ex vivo expanded autologous human corneal epithelial cells containing stem cells)<br><br>Patient/carer groups<br>• Action for Blind People<br>• Black Health Agency<br>• Blind Veterans UK<br>• Dan's Fund for Burns<br>• Eyecare Trust<br>• Fight for Sight<br>• Katie Piper Foundation<br>• Muslim Council of Britain<br>• NFBUK – The Voice of Blind People<br>• OBAC – Supporting the independence of disabled people<br>• Royal National Institute of Blind People (RNIB)<br>• SeeAbility – Seeing beyond disability<br>• Sense<br>• South Asian Health Foundation<br>• Specialised Healthcare Alliance<br>• Thomas Pocklington Trust<br><br>Professional groups<br>• Association of Anaesthetists of Great Britain and Ireland<br>• Association of Optometrists<br>• Association of Surgeons of Great Britain and Ireland<br>• British Burns Association<br>• British Geriatrics Society<br>• British and Irish Orthoptic Society | General<br>• Allied Health Professionals Federation<br>• Board of Community Health Councils in Wales<br>• British National Formulary<br>• Care Quality Commission<br>• Department of Health, Social Services and Public Safety for Northern Ireland<br>• Healthcare Improvement Scotland<br>• Medicines and Healthcare products Regulatory Agency<br>• National Association of Primary Care<br>• National Pharmacy Association<br>• NHS Alliance<br>• NHS Commercial Medicines Unit<br>• NHS Confederation<br>• Scottish Medicines Consortium<br>• Wales Council for the Blind<br><br>Possible comparator companies<br>• None<br><br>Relevant research groups<br>• British Council for Prevention of Blindness<br>• Cochrane Eyes and Vision Group<br>• Eye Hope<br>• Institute of Ophthalmology, University College London<br>• MRC Centre for Regenerative Medicine<br>• MRC Clinical Trials Unit<br>• National Eye Research Centre<br>• National Institute for Health Research<br>• UK Stem Cell Foundation |

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| • British Opthalmic Anaesthesia Society<br>• College of Optometrists<br>• Royal College of Anaesthetists<br>• Royal College of General Practitioners<br>• Royal College of Nursing<br>• Royal College of Ophthalmologists<br>• Royal College of Pathologists<br>• Royal College of Physicians<br>• Royal Pharmaceutical Society<br>• Royal Society of Medicine<br>• UK Clinical Pharmacy Association<br><br><u>Others</u><br>• Department of Health<br>• NHS Bracknell and Ascot CCG<br>• NHS England<br>• NHS Slough CCG<br>• Welsh Government | <u>Associated Public Health Groups</u><br>• Public Health England<br>• Public Health Wales |

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

***PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS***

**Definitions:**

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

## Company evidence submission

**CHHOL20170316| Date of Preparation: March 2017**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **Holoclar STA Manufacturer Submission [ID899] ACIC** | **Final (updated March 2017)** | **Yes** | **13th March 2017** |

# Contents

# Tables

# Figures

# Abbreviations

ACLSCT, Autologous cultured limbal stem cell transplantation

ADR, Adverse drug reaction

AE, Adverse event

AMT, Amniotic membrane transplantation

ATMP, Advanced therapy medicinal product

BCVA, Best corrected visual acuity

BSE, Best-seeing eye

CD, Cadaveric donor

CDVA, Corrected distance visual acuity

CLAL-CD, conjunctival limbal allograft from a cadaveric donor

CLAU, Conjunctival limbal autograft

DALK, Deep anterior lamellar keratoplasty

EQ-5D, EuroQol-Five Dimensions

EU, European Union

HRQoL, Health-related quality of life

IOP, Intraocular pressure

ITT, Intention-to-treat

KLAL, Keratolimbal allograft

LFSES, Long Form Socioemotional Scale

LFVFS, Long Form Visual Functioning Scale

LESC, Limbal epithelial stem cells

Lr-CLAL, conjunctival limbal allograft from a live related donor

LSCD, Limbal stem cell deficiency

LSCT, Limbal stem cell transplantation

LRD, Living-related donor

NEI-VFQ, National Eye Institute Visual Function Questionnaire 25

NV, Neovascularisation

NVA, Natural visual acuity

N/A, Not available or applicable

OS, Ocular surface

OSDI, Ocular Surface Disease Index

PED, Persistent epithelial defect

PKP, Penetrating keratoplasty

QALY, Quality-adjusted life year

QoL, Quality of life

RMP, Risk Management Plan

SAE, Serious adverse event

SD, Standard deviation

SJS, Stevens-Johnson syndrome

SOC, Standard of care

TBUT, Tear film breakup time

UCVA, Uncorrected visual acuity

VA, Visual acuity

WSE, Worst-seeing eye

# 1 Executive summary

The use of stem cells to regenerate and repair tissues and organs is the subject of intense scientific and media interest. Due to the practical and ethical challenges of using embryonic stem cells, the alternative of using somatic stem cells taken from the intended patient offers major advantages and allows for immediate therapeutic application.

Holoclar is the first advanced therapy medicinal product (ATMP) containing stem cells to receive a Marketing Authorisation within the EU(1) and to date there is no stem cell product with regulatory authority approval outside the EU. This breakthrough in personalised, regenerative medicine responds to an unmet medical need for a rare and seriously debilitating orphan condition called limbal stem cell deficiency (LSCD), a condition affecting one or both eyes that left untreated results in chronic pain, photophobia, inflammation, corneal neovascularisation and the reduction or complete loss of vision.

Visual loss can have a devastating impact on quality of life and is a universal fear. In the 'Eye on Eyesight' survey,(2) loss of vision is more feared by 50-64 year olds than cardiovascular disease (63% vs 37%). Indeed, 79% of people interviewed stated that, apart from their own death/death of a loved one, the loss of eyesight was the 'worst thing that could happen to me'.

Given the innovative nature of Holoclar, it offers several advantages over comparator technologies to transplant conjunctival-limbal or keratolimbal tissue in patients with LSCD, including lack of immunological rejection and hence the avoidance of immunosuppression (and the associated range of adverse events, risk of rejection and costs), the smaller amount of donor tissue required thereby reducing the risk of injury (in the case of unilateral LSCD) to the patient's own other healthy eye, the ability to treat both eyes and the possibility of retreatment if required. Holoclar also offers a bridge to subsequent successful keratoplasty for some patients with LSCD complicated by deep stromal scarring, which in turn can further significantly improve visual acuity.(3)

As well as being the first ATMP containing stem cells to receive a Marketing Authorisation in Europe, Holoclar also represents the first time that the ATMP Regulation (EC 1394/2007) has been successfully applied to a living cell-based product. However, as the development work for Holoclar was largely completed prior to the introduction of the ATMP Regulation, this required a novel Regulatory approach reliant solely upon retrospective data. Despite this, substantial numbers of patients for a rare condition (n = 148) were included in the studies of Holoclar.(3) For all these reasons, the recommendation to approve Holoclar is considered one of the most significant milestones achieved by the EMA in the last 20 years.(4)

With a known and favorable benefit-risk ratio, Chiesi UK Ltd are seeking to introduce this breakthrough medicinal product, Holoclar, to the NHS in England for the benefit of adult patients with moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus for biopsy who currently have medical needs that cannot be met by comparator technologies and where Holoclar is clinically superior and dominates over other technologies.

The proposed introduction of Holoclar also fits with the existing pathways of care for patients with LSCD within the NHS, as discussed in sections 2.4, 3.5 and 3.6. Based on the clinical findings and benefit-risk profile of this technology, its proposed place in the treatment of adult patients with moderate to severe LSCD, unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus for biopsy follows:

- For unilateral LSCD, as an alternative to CLAU in patients who are unsuitable for CLAU or who are unwilling to undergo CLAU due to concerns about damage to their contralateral healthy donor eye or in whom CLAU has failed and cannot therefore be repeated.

- For bilateral LSCD where patients have a minimum of 1-2 $mm^2$ of undamaged limbus:

    - as an alternative to KLAL in patients who do not have an available and/or willing live-related donor;

- as an alternative to lr-CLAL and KLAL in patients for whom topical and systemic immunosuppression is considered unsuitable or is undesirable; and/or

- as an alternative to lr-CLAL and KLAL in patients who require the potential for a successful treatment outcome beyond 3-5 years.

The proposed introduction of Holoclar therefore does not alter the structure of the current clinical pathway within the NHS, but provides an alternative treatment option for the patient groups referred to above.

## *1.1 Statement of decision problem*

The decision problem that this submission addresses is presented in the table below.

**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | Adults with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus | Adults with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus | N/A |
| **Intervention** | Ex vivo expanded autologous human corneal epithelial cells containing stem cells | Ex vivo expanded autologous human corneal epithelial cells containing stem cells | N/A |
| **Comparator (s)** | For people with unilateral limbal stem cell deficiency:<br>• conjunctival limbal autograft<br>• best supportive care | For people with unilateral limbal stem cell deficiency:<br>• conjunctival limbal autograft<br>• best supportive care | N/A |

| | | | |
|---|---|---|---|
| | For people with bilateral limbal stem cell deficiency:<br>• conjunctival limbal autograft<br>• limbal epithelial stem cells allografts<br>• best supportive care | For people with bilateral limbal stem cell deficiency:<br>• conjunctival limbal autograft<br>• limbal epithelial stem cells allografts<br>• best supportive care | |
| **Outcomes** | The outcome measures to be considered include:<br>• clinical parameters of limbal stem cell deficiency including stability and transparency of the corneal epithelium and superficial corneal neovascularisation<br>• symptoms of limbal stem cell deficiency including pain, burning and photophobia<br>• visual acuity (the affected eye)<br>• visual acuity (the whole person)<br>• adverse effects of treatment<br>• health-related quality of life. | The outcome measures considered include:<br>• clinical parameters of limbal stem cell deficiency including stability and transparency of the corneal epithelium and superficial corneal neovascularisation<br>• symptoms of limbal stem cell deficiency including pain, burning and photophobia<br>• visual acuity (the affected eye)<br>• visual acuity (the whole person)<br>• adverse effects of treatment<br>• health-related quality of life. | N/A |

| | | | |
|---|---|---|---|
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye. | For the reference case, the cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year.<br>The time horizon for estimating clinical and cost effectiveness is over the lifetime of the patient, i.e. sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs are considered from an NHS and Personal Social Services perspective.<br>The cost effectiveness analysis includes consideration of the benefit in the best and worst seeing eye. | N/A |
| **Subgroups to be considered** | Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye. | Two subgroups are considered:<br>• Patients with bilateral limbal stem cell deficiency who have | |

| | | | |
|---|---|---|---|
| | | their worst seeing eye treated<br>• Patients with bilateral limbal stem cell deficiency who have their best seeing eye treated | |
| **Special considerations including issues related to equity or equality** | | For Armed Forces personnel who acquire moderate to severe LSCD due to physical or chemical ocular burns sustained during service, e.g. due to explosive devices, the impact of LSCD in this group (unilaterally or bilaterally) may be further complicated by concomitant loss of limb and other life-threatening or life-changing injuries. As such, this group is disproportionately affected by physical disabilities, and other mental health sequelae, which differ to the general population of patients with moderate to severe LSCD due to physical or chemical | Armed Forces Covenant (5) |

| | | | |
|---|---|---|---|
| | | ocular burns. A significant equality issue may therefore be created if Holoclar is not recommended for use within the NHS in England, contrary to the Armed Forces Covenant. | |

## *1.2 Description of the technology being appraised*

The Holoclar Summary of Product Characteristics and European Product Assessment Reports are provided as Appendix 1 and Appendix 2 respectively and contain detailed descriptions of the technology.

**Table 2: Technology being appraised**(6)

| | |
|---|---|
| **UK approved name and brand name** | Holoclar▼ 79,000-316,000 cells/cm$^2$ living tissue equivalent (ex vivo expanded autologous human corneal epithelial cells containing stem cells) |
| **Marketing authorisation status** | The European Commission granted a conditional Marketing Authorisation (EU/1/14/987/001) valid throughout the European Union on 17$^{th}$ February 2015. |
| **Indications and any restriction(s) as described in the summary of product characteristics** | **Indication:** Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2 mm$^2$ of undamaged limbus is required for biopsy.<br>**Contraindications:** Hypersensitivity to any of the product's excipients or to bovine serum and murine 3T3-J2 cells. |
| **Method of administration and dosage** | Holoclar is administered by implantation. Full technical details on the procedures associated with the use of Holoclar are provided in the educational manual for the screening and treatment of pre- and post-operative patients undergoing an autologous transplant of the |

| | |
|---|---|
| | corneal epithelium reconstructed from stem cells (see Appendix 3). |

## *1.3 Summary of the clinical effectiveness analysis*

Systematic literature reviews, as described in sections 4.1 and 4.2, have identified no RCTs relevant to this technology appraisal, as is to be expected with a rare, orphan indication for which until recently no medicines have been developed or received Marketing Authorisation. For the comparator technologies of conjunctival limbal autograft (CLAU), limbal epithelial stem cells allografts (CLAL and KLAL) and best supportive care, a small number of published retrospective, observational case series often with small patient numbers, different patient selection criteria (including patients with LSCD not caused by ocular burns), different operative techniques performed by different surgeons at different centres, different post-surgical aftercare and with short follow-up periods, have been identified. To further complicate the evidence base, these case series have been collected over a 30 year period, during which there has been significant developments and progress in transplantology, including what is considered to be best supportive care, and this evidence base is subject to significant bias, including selection bias, assessment bias and likely publication bias.

Whilst the pivotal trial for Holoclar, HLSTM01,(7) is also observational in nature it has a relatively large sample size (n=104 patients), was conducted in a homogeneous population all of whom were operated on at two surgical sites using standardised selection criteria and post-operative care. Patients included in this study were also followed-up over a long period of time (maximum 10 years). This leads to an unusual situation in which there is substantially more robust evidence regarding the new technology, Holoclar, than there is regarding the identified established comparators. This is further supported by the appraisal of the evidence, quality assessments and bias assessment undertaken in sections 4.11.2, 4.11.3 and 4.11.4 respectively.

Due to the nature of these data it is therefore not possible to formally compare, either directly or indirectly, the alternative technologies to treat adult patients with moderate to severe LSCD, unilateral or bilateral, due to physical or chemical ocular burns and

the limitations of the evidence base make it difficult to generate definitive conclusions either for individual technologies or across the different treatment modalities.

For the two key efficacy outcomes, ocular stability and visual acuity, which are discussed in section 4.11, the percentage of patients achieving ocular stability and/or improvement in visual acuity is shown in table 3 below:

**Table 3: Summary of key clinical efficacy findings**

| Technology | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in visual acuity |
|---|---|---|
| Holoclar | 60-78% | 40-71.4% |
| CLAU | 66.7-100% | 20-100% |
| CLAL/KLAL | 60-80% | 65-100% |

However, the duration of follow-up in the case series reported for the comparator technologies is variable, compared to Holoclar is relatively short and the clinical data may not therefore accurately capture the clinical effects observed in the long-term or the extent of longer-term treatment failures. What is also clear from the studies of Holoclar is that if Holoclar remains successful at 12-months post-operatively, then this technology is likely to remain successful and published data supports the success of Holoclar in this scenario up to 14.5 years post-operatively.(8)

The safety profile of Holoclar is also well documented both quantitatively and qualitatively, in contrast to that of the comparator technologies where the reporting and description of adverse events is sporadic (see section 4.12). Safety data from Holoclar are taken from the pooled findings of the three Holoclar trials, one of which was a specific study of safety. The benefit-risk balance for Holoclar in the treatment of adult patients with moderate to severe LSCD, unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus for biopsy, is therefore considered favorable. This view is supported by the grant of a Marketing Authorisation for Holoclar in this indication on 17th February 2015.(6)

## *1.4 Summary of the cost-effectiveness analysis*

Two Excel models are constructed to capture the cost and QALY consequences of treatment of unilateral and bilateral LSCD by Holoclar, CLAU, lr-CLAL and KLAL over a life-time duration. Each model consists of a decision tree initial treatment phase which permits biopsy and transplant success and failure and re-transplant where appropriate followed by a yearly Markov structure which permits states stable state; failed BSC state and death. At year one keratoplasty surgery is incorporated for a proportion of patients with stromal scarring and successful transplant.

Tables 4 and 5 (below) show the base case results with final ICERs for all options and ICERs with and without the CLAU treatment option. The presentation of results with and without CLAU is particularly informative in the bilateral case as current treatment algorithms all omit CLAU as a plausible treatment for bilateral LSCD.(9–11)

Base case results for both unilateral and bilateral LSCD suggest that CLAU dominates all other treatment options. However in the absence of CLAU and for cases where it may not be applicable, such as all bilateral cases, or where refused by the patient, Holoclar is the most cost-effective option.

The key driving forces of the economic arguments are the long-term improvement in utility and the potential for substantial offset costs. In terms of utility gains, the main mechanism of incremental QALY gain is via improvement in disfigurement followed by improvement in the visual acuity of the WSE in the unilateral case and both eyes in the bilateral case. Although there is uncertainty regarding the contribution to overall utility made by the VA of the WSE, the results are robust to changes in VA to utility mapping alternatives as well as differing weights applied to WSE VA. The contribution of VA based utility to overall incremental QALYs (relative to baseline) is substantial as eyes may improve from very poor VA to VA with little impairment with an effect that is maintained over a long time period due to the age of prevalent patients (base case). This contribution is increased if we consider the average age of the incidence patient. The utility argument is supplemented by reductions in pain/burning/photophobia though these have a minor impact.

**Table 4: Unilateral LSCD base case results**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 22,158 | 12.64 | | | Dominates | Dominates | |
| Ir-CLAL | £ 77,434 | 9.73 | £ 27,313 | -2.92 | Dominates | | |
| KLAL | £ 89,256 | 9.80 | £ 3,256 | 0.07 | Dominates | | |
| HOLOCLAR | £ [redacted] | 12.09 | £ [redacted] | 2.29 | Dominates | | £ 7,185 |
| BSC | £ 101,535 | 7.18 | £ 18,610 | -4.91 | | | |

**Table 5: Bilateral LSCD base case results**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 47,402 | 10.08 | | | Dominates | Dominates | |
| Ir-CLAL | £ 155,430 | 6.36 | £ 108,029 | -3.72 | Dominates | | |
| KLAL | £ 173,844 | 6.56 | £ 18,414 | 0.20 | Dominates | | |
| HOLOCLAR | £ [redacted] | 9.25 | £ [redacted] | 2.69 | Dominates | | £ 12,438 |
| BSC | £ 193,323 | 2.44 | £ 1,906 | -6.81 | | | |

In terms of costs, the most substantial transplant cost is that of the product cost of Holoclar. In addition major eye operations and the following after-care also generate costs in the thousands, but these are applicable to all transplants. Nevertheless expensive upfront costs are offset by reductions in the costs of treatment in BSC which via the need for autologous serum eye drops can be substantial. Our base case model assumes an annual cost of £3,758 though one expert opinion suggested that 'BSC typically costs the NHS £7,500 per annum'. As with the QALY gain the offset costs may persist over a long period giving plenty of opportunity to more than offset any high upfront costs.

With high published rates of mainly short-term success rates all treatments for both unilateral and bilateral LSCD dominate BSC in the base case analysis. For both unilateral and bilateral LSCD, CLAU and Holoclar are found to be more cost-effective than lr-CLAL and KLAL due to the failure rates over time of the allograft alternatives. Literature reviews and expert opinion suggest only temporary benefits (maximum 3-5 years) for many initially successful allograft transplants.

Systematic literature reviews revealed there are no RCTS and only a small number of observational studies often with small numbers of patients and with short follow-up periods. There is no possibility of formal direct or indirect comparisons for the alternative transplant treatments and BSC. And whilst the pivotal trial for Holoclar is also observational in nature it has a relatively large sample size followed over a long period (maximum 10 years). This leads to a slightly unusual situation in which there is substantially more robust evidence about the new treatment than there is regarding the established alternatives. Nevertheless the paucity of the evidence base makes it difficult to produce definitive certain results across treatments.

The model was subjected to a wide range of sensitivity tests and the results remained largely robust to very different alternative values: CLAU is the most cost-effective procedure followed by Holoclar. The reasons for this are not hard to untangle, due to the average age of patients then any successful treatment that persists over time is likely to deliver a substantial life-time incremental QALY gain and offset BSC treatment costs which would otherwise persist over time. The duration of effect is sufficient to overcome very different alternatives in terms of QALY generation (very different VA to QALY mapping algorithms for example.)

In conclusion, although there are considerable sources of uncertainty, the model is relatively robust to alternative model assumptions in key areas and consistently finds that CLAU, followed by Holoclar then followed by the allografts are all cost-effective relative to BSC in that order. These results apply to both unilateral and bilateral LSCD, though as the use of CLAU in bilateral LSCD is not adopted in practice, Holoclar is the most cost-effective of the plausible treatments. The single biggest driving factor of that result is the modelled duration of effectiveness, for which the best supporting evidence is provided by Holoclar.

# 2 The technology

## *2.1 Description of the technology*

The subject of this submission is an Advanced Therapy Medicinal Product called Holoclar 79,000-316,000 cells/cm$^2$ living tissue equivalent. The brand name of this technology is Holoclar and the international non-proprietary name (INN) is ex vivo expanded autologous human corneal epithelial cells containing stem cells. This product belongs to the pharmacotherapeutic group of Ophthalmologicals: other ophthalmologicals and has an ATC code of S01XA19.(6)

Holoclar is manufactured from a biopsy taken from a small area of undamaged limbus of the patient's eye. After non-specific isolation of the cells, they are expanded in cell culture under specific culture medium conditions and are seeded on a layer of an irradiated 3T3-J2 mouse feeder cell line. Prior to Holoclar release, the expanded cell suspension is cryopreserved until a transplantation date is scheduled. Holoclar is therefore composed of a thawed suspension of a heterogeneous mixture of ex vivo expanded sub-confluent autologous human corneal cells in medium, with the potential to form a stratified epithelium.(6)

The active substance contains a minimum of small-sized limbal epithelial stem cells, as determined histochemically by expression of the phenotypic marker p63 bright at release ('holoclones'). Beside these p63++ cells, the keratinocyte culture also contains clonogenic transiently amplifying (TA) cells ('meroclones' and 'paraclones'), and terminally differentiated non-clonogenic corneal epithelial (K3+) cells.(3)

Holoclar is defined as autologous tissue-engineered product which consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm$^2$), expanded ex vivo, including on average 3.5% (0.4% to 10%) limbal stem cells, stem cell-derived transient amplifying and terminally differentiated cells, prepared from a limbus biopsy of the patient as starting material, and attached on a 2.2 cm diameter fibrin support and maintained in physiological transport.(3)

The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular

burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium.(6)

The p63++ stem cell subset forming holoclones is considered to be the main functional component of Holoclar, since these cells are expected to mediate long-term efficacy. The issue of potency is therefore addressed by quantification of p63++ cells. Further differentiated cell populations are considered as supportive, but functionally contributing cells for short/medium-term efficacy.(3)

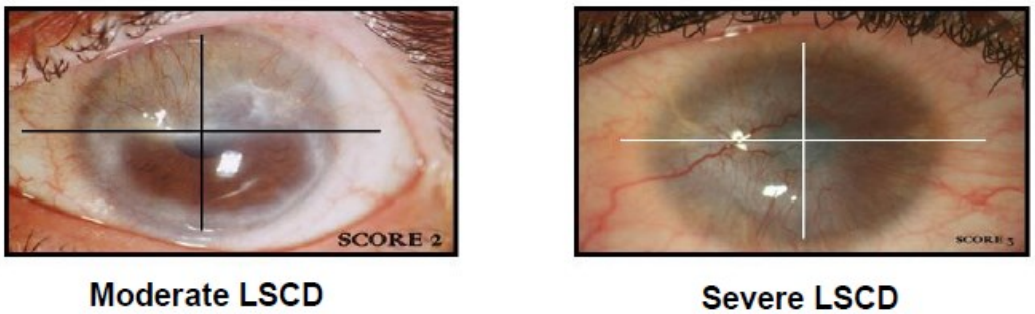
Further details of the technology can be found in the Holoclar Summary of Product Characteristics and European Assessment Report, see Appendix 1 and Appendix 2.

## *2.2 Marketing authorisation and health technology assessment*

On 18 December 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a conditional Marketing Authorisation for the medicinal product Holoclar.(1) The European Commission granted a Marketing Authorisation valid throughout the European Union for Holoclar on 17 February 2015.(6)

The authorised indication of Holoclar is for the treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2 $mm^2$ of undamaged limbus is required for biopsy.(6)

**Figure 1: Photographic illustration of moderate and severe LSCD**



Contra-indications to Holoclar include hypersensitivity to any of the product's excipients, which include the transport medium (Dulbecco's Modified Eagles Medium supplemented with L-glutamine) and the fibrin support, or to bovine serum and murine 3T3-J2 cells.(6)

Holoclar is intended for autologous use only and must be administered by an appropriately trained and qualified surgeon. Holoclar is restricted to hospital use only.(6)

Both the current approved Summary of Product Characteristics (10th December 2015) and the European Public Assessment Report for Holoclar are included as part of this submission, see Appendix 1 and Appendix 2 respectively.

The main issues discussed by the regulatory authorities during the Marketing Authorisation application process were as follows:(3)

- A major objection was raised regarding the murine 3T3 feeder layer and the requirement for demonstration of non-proliferation of the cell line after irradiation. This was successfully addressed by validation of the irradiation method and the introduction of an additional control test for residual 3T3-J2 cells in the finished product.

- A major objection was raised regarding the microbiological control strategy during the manufacturing process. All issues regarding control of microbiological safety were successfully addressed by implementation of appropriate in-process controls for microbial contaminations and validated rapid detection methods for the identification of microbial contaminations before product release and administration.

- The final product, Holoclar, has a shelf life of 36 hours and is vulnerable and sensitive to mechanical and temperature stress. All concerns regarding stability and transport for the finished product were successfully addressed by an accurate and reliable stability evaluation, together with the implementation of a strict and robust container closure system and tight control of transport conditions to ensure product quality.

- The evaluation of efficacy of Holoclar was based on retrospective analyses of a comparably large set of data given the rarity of the disease. Despite the disadvantages of such study design, overall, the data were considered of sufficient quality to support establishment of a beneficial treatment effect, thereby enabling early availability to patients via a conditional Marketing Authorisation. Such early availability was considered to be in the interest of public health given that LSCD is a serious debilitating disease for which no authorised treatment exists in the European Union. Available data were considered insufficient to draw final conclusions for paediatric populations.

  Nevertheless, for a comprehensive clinical dataset, prospectively collected data are needed in order to confirm the treatment benefits observed in the retrospective analyses, in particular since it could not be excluded that bias has been introduced as a result of the retrospective study design. Therefore Chiesi will, as a condition of Marketing Authorisation, conduct a prospective, multinational, multicentre, open label, uncontrolled interventional phase IV study, HLSTM03/HOLOCORE,(12) in at least 65 patients (plus 5 paediatric patients as agreed in the approved Paediatric Investigation Plan) with moderate to severe LSCD. However, the CAT considers the following measures necessary to address the missing efficacy data in the context of a conditional MA.

- The safety evaluation of Holoclar was based on a comprehensive analysis covering the time from biopsy procedure for limbal stem cell harvest through transplantation of Holoclar up to the end of follow up, with particular attention to a possible relation of adverse events with concomitant anti-inflammatory and antibiotic medications. Adverse reactions observed were mainly eye related and generally manageable. From the data submitted, no major safety concerns emerged.

  However, the following measures were considered necessary to address missing safety data in the context of a conditional Marketing Authorisation:

  1. A multinational, multicentre, prospective, open-label, uncontrolled interventional study, HLSTM03/HOLOCORE,(12) to assess the efficacy

and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns.

2. A long-term safety and efficacy follow-up after autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns (HLSTM03-FU).(13)

3. Post-authorisation Registry entitled 'Long-term safety after Holoclar implant for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns: observational study of routine clinical practice, HLSTM05/HOLOSIGHT.(14)

These conditional efficacy and safety measures have already been put in place by Chiesi, although these studies and the Registry will not contribute additional data within the context of this technology appraisal or the subsequent 12 months. Further information regarding the issues discussed by the regulatory authorities can be found in the EPAR, see Appendix 2.

Holoclar has not yet been launched in the UK. [redacted]. Given the Marketing Authorisation for Holoclar is valid throughout the European Union, Holoclar has regulatory approval outside the UK in the other 27 member states of the European Union. Holoclar has not yet been granted regulatory approval in other countries outside of the European Union.

Holoclar is not currently subject to any other health technology assessment in the UK.

## *2.3 Administration and costs of the technology*

In order to manufacture Holoclar, a biopsy is first required to obtain autologous limbal stem cells from the patient for culture and expansion. The finished product, Holoclar, is then administered to the patient by implantation by an appropriately trained and qualified surgeon and is restricted to hospital use only.(6)

*Biopsy*(6)

For the manufacture of Holoclar, a biopsy of 1-2 $mm^2$of undamaged limbus is required. The biopsy is performed using topical anaesthesia. The eye is subjected to ocular surface lavage with sterile balanced saline solution for eye irrigation followed by detachment of the conjunctiva from the limbus to expose the sample collection site of the cornea. An incision of 2 x 2 mm is made to remove the biopsy. The biopsy is placed in the sterile test tube supplied containing transport medium. The biopsy must be received by the manufacturer within 24 hours from the procurement. Following the biopsy, an appropriate regimen of prophylaxis with an antibiotic treatment must be given.

In some cases it may be possible that the source limbal stem cells of the patient are not expandable or that the release criteria are not met, due to poor biopsy quality, patient characteristics or manufacturing failure. Therefore, it can occur that Holoclar cannot be delivered. The surgeon will be informed as early in the process as possible so that another biopsy may be considered for the patient.

*Implantation*(6)

Holoclar is intended solely for use in autologous limbal stem cell regeneration in line with the approved therapeutic indication and should be administered under aseptic conditions in conjunction with limbal peritomy, undermining of the conjunctiva and excision of the corneal fibrovascular tissue in preparation of the defect bed. Next, the insert is fitted under the undermined conjunctiva. The excess of insert is trimmed and the edge covered with the conjunctiva applying 2 or 3 stitches (sutures) of vicryl or silk 8/0 in order to form a physical seal of the lesion and to secure the implant. The eyelids are kept closed over the insert with a steri-strip band. Holoclar is generally implanted under topical retrobulbar or parabulbar anaesthesia. Other anaesthesiology procedures may be followed at the discretion of the surgeon.

The amount of cells to be administered is dependent on the size (surface in $cm^2$) of the corneal surface. Each preparation of Holoclar contains an individual treatment dose with sufficient number of cells to cover the entire corneal surface. The recommended dose of Holoclar is 79,000-316,000 cells/$cm^2$, corresponding to 1 $cm^2$ of product/$cm^2$ of defect. Each preparation of Holoclar is intended as a single

treatment. The treatment may be repeated if considered indicated by the treating physician.

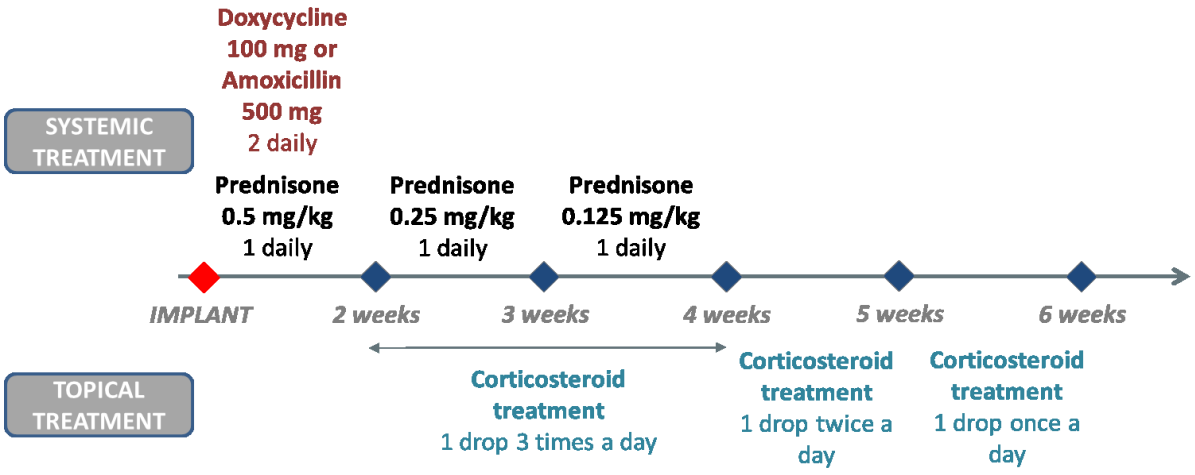
*Post-operative treatmen*t(6)

Following implantation, an appropriate regimen of topical and systemic anti-inflammatory and prophylactic antibiotic treatment must be given. The following regimen is suggested:

Doxycycline 100 mg tablets twice daily (or amoxicillin 500 mg twice daily) and prednisone orally at a daily dose of 0.5 mg/kg (to a maximum dose of 25 mg) per day should be administered from the day of surgery for 2 weeks. After 2 weeks the systemic antibiotic administration should be stopped and the daily dose of prednisone should be tapered to 0.25 mg/kg (maximum 12.5 mg) per day for 1 week, to 0.125 mg/kg (maximum 5.0 mg) per day for the following week and then stopped.

Two weeks after surgery, a topical corticosteroid treatment should be started with preservative-free dexamethasone 0.1% eye-drops, 1 drop three times per day for 2 weeks, then reduced to 1 drop twice daily for 1 week and 1 drop once daily for a further week. The topical corticosteroid can be maintained in case of persistent ocular inflammation. The post-implantation regime of combination topical and systemic anti-inflammatory and prophylactic antibiotic treatments is summarised in figure 2 below.

**Figure 2: Regime for post-implantation combination treatment**



Implantation of Holoclar must be followed by an appropriate clinical monitoring schedule. Follow-up visits should be performed according to clinical judgement. Follow-up visits at 3 days, 14 days, 45 days, 6 months and 12 months are suggested but not imposed.

Full technical details on the procedures associated with the use of Holoclar are provided in the educational manual for the screening and treatment of pre- and post-operative patients undergoing an autologous transplant of the corneal epithelium reconstructed from stem cells, see Appendix 3.

*Cost*

The acquisition cost (list price) for Holoclar is £80,000 (ex VAT) per treatment per eye.(15) Within the terms of the Holoclar patient access scheme, this price is reduced [redacted] for all NHS patients treated with Holoclar within an NHS setting. This cost includes:

- A full training program for surgeon and NHS staff.
- Shipment of the biopsy from the treatment centre to the production facility under controlled conditions.
- Storage of the biopsy in a controlled environment and according to strict privacy-protecting Standard Operating Procedures.
- Freezing and storage of the biopsy, giving the potential for a second Holoclar to be manufactured from the same biopsy.
- Ex-vivo GMP culturing and expansion of the biopsy cells, testing for potency and approval under conditions of Good Laboratory Practice.
- Shipment and delivery of the final product to the treatment centre under controlled conditions.

In addition to the manufacture of Holoclar, Chiesi also provide (at no additional cost) the following integrated services and logistics to support the use of Holoclar. Indeed, Chiesi undertake and guarantee all logistical aspects associated with shipment of biopsies to the manufacturing facility as well as the manufacturing and shipment of

Holoclar to all treatment centres. The key elements of Chiesi's integrated services are:

- Preparation of the stakeholders involved through a system of procedures, training and certifications.
- Training of the surgeons that will use Holoclar to support optimal use of Holoclar and standardisation of the surgical procedure.
- Planning, procurement (transport within 24 hours), production and distribution (within 36 hours) for each individual patient with a "case manager" dedicated to each product.
- Management of the stakeholders involved through a dedicated Customer Service.
- Real-time tracking of Holoclar shipments (dedicated transport at a constant temperature with refrigeration, geolocation and continuous monitoring of temperature, humidity and pressure.

Chiesi has formally submitted a patient access scheme for Holoclar with the Department of Health. Application for this patient access scheme was referred by the Department of Health to the Patient Access Schemes Liaison Unit (PASLU) on 1st December 2016 for inclusion in this technology appraisal. This patient access scheme comprises a simple discount scheme applicable to all NHS supplies and preparations of Holoclar and is valid for all current and future indications (for the duration of the Patient Access Scheme) and in all NHS settings, whereby the acquisition cost of Holoclar is reduced [redacted] with no conditions other than needing to be agreed as a confidential discount scheme with the NHS for NHS patients only. The costs of Holoclar are summarised in table 4 below.

**Table 4: Costs of the technology being appraised**

| | Cost | Source |
|---|---|---|
| **Pharmaceutical formulation** | Implantable stem cell therapy | Holoclar Summary of Product |

| | | |
|---|---|---|
| | | Characteristics(6) |
| **Acquisition cost (excluding VAT) *** | Holoclar list price: £80,000 per treatment per eye<br>Holoclar patient access scheme price: [redacted]<br><br>Acquisition cost of combination treatments:<br>Oral doxycycline 100mg bd for 2 weeks = £3.01<br>Oral amoxycillin 500,g bd for 2 weeks = £1.69<br>Oral prednisolone for 4 weeks = £10.83<br>Topical dexamethasone for 4 weeks = £13.58 | Department of Health letter, 29th November 2016 (15)<br><br>For combination treatments MIMS Online(16) |
| **Method of administration** | Implantation | Holoclar Summary of Product Characteristics(6) |
| Doses | The amount of cells to be administered is dependent on the size (surface in cm²) of the corneal surface. Each preparation of Holoclar contains an individual treatment dose with sufficient number of cells to cover the entire corneal surface. The recommended dose of Holoclar is 79,000 – 316,000 cells/cm², corresponding to 1 cm² of product/cm² of defect. The product is trimmed to match the exact size of the individual patient's cornea by the administering surgeon. Each preparation of Holoclar is intended as a single treatment. | Holoclar Summary of Product Characteristics(6) |
| **Dosing frequency** | Each preparation of Holoclar is intended as a single treatment. The treatment may be repeated if considered indicated by the treating physician. | Holoclar Summary of Product Characteristics(6) |

| | | |
|---|---|---|
| **Average length of a course of treatment** | Single administration | Holoclar Summary of Product Characteristics(6) |
| **Average cost of a course of treatment** | Holoclar list price: £80,000 (ex VAT) per treatment per eye<br>Holoclar patient access scheme price: [redacted] | Department of Health letter, 29th November 2016(15) |
| **Anticipated average interval between courses of treatments** | Holoclar treatment may be repeated if considered indicated by the treating physician, therefore the average interval between courses of treatments is anticipated to be variable | Holoclar Summary of Product Characteristics(6) |
| **Anticipated number of repeat courses of treatments** | It is anticipated that 10% of patients will require one re-treatment with Holoclar and 1% will require two re-treatments with Holoclar | Trial data HLSTM01(7) |
| **Dose adjustments** | None | Holoclar Summary of Product Characteristics(6) |
| **Anticipated care setting** | Holoclar must be administered by an appropriately trained and qualified surgeon and is restricted to hospital use only | Holoclar Summary of Product Characteristics(6) |
| * Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented. | | |

## *2.4 Changes in service provision and management*

Current service provision, funded by NHS England and in place under current contracts, provides the pre-surgical management and screening and post-surgical interventions, monitoring and follow-up required to support the use of any LSC transplant procedure, including the proposed introduction of Holoclar. The introduction of Holoclar is not expected to alter the current healthcare resource use

and associated costs, nor require any additional infrastructure requirements beyond those already in place and that support established clinical practice in England.

Currently LSC transplantation takes place in and is subsequently followed-up and managed by hospital tertiary referral centres specialising in ophthalmology. Again, this will be unchanged for the proposed introduction of Holoclar. The only difference is that given the rarity of moderate to severe LSCD due to ocular burns in adults (as opposed to all causes of LSCD), treatment with Holoclar will take place in two specialist treatment centres in Newcastle and London. This ensures that specialist surgical skill and expertise is developed and maintained despite the rarity of this condition and provides for regional coverage. The use of Holoclar will also be commissioned by NHS England specialised services.(17)

Concomitant therapies specified in the Marketing Authorisation of Holoclar are as follows:(6)

- Doxycycline 100 mg tablets twice daily (or amoxicillin 500 mg twice daily) and prednisone orally at a daily dose of 0.5 mg/kg (to a maximum dose of 25 mg) per day should be administered from the day of surgery for 2 weeks.

- After 2 weeks the systemic antibiotic administration should be stopped and the daily dose of prednisone should be tapered to 0.25 mg/kg (maximum 12.5 mg) per day for 1 week, to 0.125 mg/kg (maximum 5.0 mg) per day for the following week and then stopped.

- Two weeks after surgery, a topical corticosteroid treatment should be started with preservative-free dexamethasone 0.1% eye-drops, 1 drop three times per day for 2 weeks, then reduced to 1 drop twice daily for 1 week and 1 drop once daily for a further week. The topical corticosteroid can be maintained in case of persistent ocular inflammation.

## *2.5 Innovation*

The use of stem cells to regenerate and repair tissues and organs is the subject of intense scientific and media interest. Due to the practical and ethical challenges of using embryonic stem cells, the alternative of using somatic stem cells taken from

the intended patient offers major advantages and allows for immediate therapeutic application.

Holoclar is the first ATMP containing stem cells to receive a Marketing Authorisation in Europe.(1) To date there is no stem cell product with regulatory authority approval outside the EU. This breakthrough in personalised, regenerative medicine responds to an unmet medical need for a rare and seriously debilitating orphan condition called limbal stem cell deficiency (LSCD), a condition affecting one or both eyes that left untreated results in chronic pain, photophobia, inflammation, corneal neovascularisation and the reduction or complete loss of vision.

Visual loss can have a devastating impact on quality of life and is a universal fear. In the 'Eye on Eyesight' survey,(2) loss of vision is more feared by 50-64 year olds than cardiovascular disease (63% vs 37%). Indeed, 79% of people interviewed stated that, apart from their own death/death of a loved one, the loss of eyesight was the 'worst thing that could happen to me'.

Given the innovative nature of Holoclar, it offers several advantages over comparator technologies to transplant conjunctival-limbal or keratolimbal tissue in patients with LSCD, including lack of immunological rejection and hence the avoidance of immunosuppression (and the associated range of adverse events, risk of rejection and costs), the smaller amount of donor tissue required thereby reducing the risk of injury to living donor eyes be they the patient's own other healthy eye or the healthy eye of a relative, the ability to treat both eyes and the possibility of retreatment if required. Holoclar may also offer a bridge to subsequent successful keratoplasty for some patients with LSCD complicated by deep stromal scarring, which in turn can further significantly improve visual acuity.(3)

As well as being the first ATMP containing stem cells to receive a Marketing Authorisation in Europe, Holoclar also represents the first time that the ATMP Regulation (EC 1394/2007) has been successfully applied to a living cell-based product. However, as the development work for Holoclar was largely completed prior to the introduction of the ATMP Regulation, this required a novel Regulatory approach reliant solely upon retrospective data, yet despite this substantial numbers of patients for a rare condition (n = 148) were included in the studies of Holoclar.(3)

For all these reasons, the recommendation to approve Holoclar is considered one of the most significant milestones achieved by the EMA in the last 20 years.(4)

Furthermore, Holoclar has recently won a prestigious and independant award in innovation and research – the UK Prix Galien Orphan Product award. A Prix Galien award is widely regarded as the highest distinction to bestow upon a pharmaceutical product and is internationally recognised, with awards carried out in 17 countries as well as an international award every two years.(18)

*Impact of innovation that could be still unquantified*

The ultra-orphan nature of this technology also raises the obvious and known issue of evidence generation. It also creates the well-known issues of a need to spread high technology development fixed costs across a small population, whilst at the same time ensuring equality of access to effective treatments for patients unfortunate enough to be in orphan conditions.

The innovative nature of the technology may also lead to high early-developer development costs. The learning curve for the delivery of regenerative technologies may be steep, though future development lessons may be learned through the process. It is well known that the current NICE reference case model focuses on the current cost-effectiveness (albeit with future costs and benefits discounted to Net Present Value) but does not incorporate the future benefits that may only be made possible by setting the correct incentives for truly innovative technologies such as this. NICE themselves recognise the huge challenges in capturing all the relevant components for assessing regenerative medicine and are assessing whether the current reference case model is fit for purpose.(19)

These two issues, regenerative technology for an ultra-orphan condition, make the economic modelling extremely challenging and may not be adequately assessed by the standard reference case model.

In their DSU report of valuing pharmaceutical innovation in the process of HTA,(20) find that “Some concerns have been expressed that an assessment of value based on cost-effectiveness will not recognise the potential value of an innovative technology, i.e. one that is likely to lead to the development of more valuable future

technologies or use of the technology in other indications in the future." And that "It is commonly the case that some innovations today will provide the basis for subsequent innovations which may be even more valuable in the future."

By focusing solely on the cost per QALY and perhaps influenced by the currently limited evidence base, although it should be noted that the pivotal study of Holoclar(7) provides the strongest evidence base amongst alternatives, and rejecting the opportunity to reimburse Holoclar, decision makers may omit to consider the negative signals it sends to manufacturers of other stem-cell technologies that might be in early development or the investors that provide the capital to develop these ground-breaking technologies.

As Andrew Dillon himself puts it "Concentrating only on QALYs means we are in danger of losing sight of other things that people, health systems and the government value very highly. This includes encouraging an innovative UK research base, or perhaps valuing more highly specific treatments that may be the only option for people with certain conditions. These aspects are not captured by the QALY which is why our committees have never used QALYs as the sole determinant in their decisions." And "when you decide to move with the cutting edge of medicine, that there's a price to pay".(21)

From the patient population for HLSTM01 and estimated numbers of incident and prevalent population it is clear that there is a substantial unmet need. The patient population of HLSTM01 had an average duration of 18.3 years, and a maximum of 72.3 years, between injury and treatment by Holoclar.(7) Alternative treatments CLAU, lr-CLAL and KLAL have all been available during much of this time period and yet have either not been used or have failed for these patients. The high long-term success rate of Holoclar in HLSTM01 within a patient population with unmet need illustrates the point that this is a new technology for patients who have no effective alternative.

Apart from transplant failure one reason why CLAU may not have been successfully employed is that there is a theoretical risk that extracting large segments of conjunctivolimbal tissue from the donor eye may induce LSCD or other complications in the previously healthy eye, making some patients with unilateral LSCD unwilling to

undergo this procedure, although evidence from the literature and expert opinion suggests that iatrogenic LSCD is a rare adverse event and has only been reported in a patient undergoing CLAU for LSCD induced by chronic contact lens use.(22)

In the reference case economic model the consequences of biopsy-induced LSCD can be captured by multiplying the QALY and cost consequences by the probability of occurrence. However this approach implicitly adopts a risk-neutral perspective to the QALY consequences. If patients are risk-averse to conceding damage in their remaining good eye then the costs of this risk are above and beyond that captured by a simple QALY calculation. As the surface area of the biopsy extracted for Holoclar is considerably smaller than that needed for CLAU, the risk of inducing LSCD in the donor eye will be smaller and thus lead to additional benefits than captured by QALYS alone. One such example might be that Holoclar becomes a viable option for patients who regard the option of CLAU as too risky despite the expected benefits.

*Health-related benefits missed in the QALY calculation*

For military personnel injured in action (e.g. due to explosive devices) the impact of ocular burns and loss of vision (unilaterally or bilaterally) can be further complicated by concomitant loss of limb and other life-threatening or life-changing injuries. As such in this group, they are disproportionately affected by physical disabilities, and other mental health sequelae, which differ to the general population of patients with physical or chemical burns.

The impact of visual loss in patients with these life-changing disabilities, both physical and mental, means that the benefits from Holoclar might not be fully captured in the QALY calculation in this population, due to that this group would be disproportionately affected by these concomitant conditions. It is therefore likely that the return of sight, or improvement of visual acuity would have more of an impact in patients with a physical disability that also restricts their ability to self-care, and lead as normal a life as possible.

# 3 Health condition and position of the technology in the treatment pathway

## *3.1 Overview of LSCD*

### *3.1.1 Aetiology of moderate to severe LSCD*

The corneal epithelium is composed of stratified squamous epithelium from which superficial terminal cells are naturally and continuously shed and replaced. LSCD is characterised by a loss or deficiency of the progenitor stem cells located in the limbus that are vital for re-population of the corneal epithelium and to the barrier function of the limbus. When these stem cells are lost, the corneal epithelium is unable to repair and renew itself. This results in epithelial breakdown and recurrent or persistent epithelial defects, conjunctivalisation of the corneal surface with neovascularisation, chronic inflammation and corneal scarring. All of these contribute to loss of corneal transparency, potential visual loss, chronic pain and burning, photophobia and keratoplasty failure. In severe LSCD, part of the cornea, usually including the pupillary area, is covered by a thick fibrovascular pannus.(23)

LCSD may result from direct injury to the limbal stem cells, destruction of the limbal stem cell niche, or both.(24) It can be caused by a wide variety of primary (inherited) and secondary (external) causes summarised in Table 7.(25–28) More rarely there are idiopathic (unknown) causes.(25,29)

**Table 7. Aetiology of LSCD**(25)

| Primary causes | Secondary causes |
|---|---|
| Aniridia<br><br>Multiple endocrine deficiency<br><br>Epidermal dysplasia, e.g. Ectrodactyly-ectodermal-dysplasia-clefting syndrome<br><br>Congenital erythrokeratodermia<br><br>Dyskeratosis congenita | Thermal/Physical or chemical burns<br><br>Contact lens wear<br><br>Inflammatory eye disease:<br>• SJS, toxic epidermal necrolysis<br>• Ocular cicatricial pemphigoid<br>• Chronic limbitis: autoimmune disease, extensive microbiological infection, atopic conjunctivitis<br><br>Neurotrophic keratitis |

| | |
|---|---|
| | Extensive limbal cryotherapy, radiation, or surgery<br><br>Bullous keratopathy<br><br>Topical antimetabolites (5-Fluorouracil, Mitomycin C)<br><br>Systemic chemotherapy (Hydroxyurea) |

A most common cause of primary LSCD is aniridia (meaning no iris).(25,30) Aniridia is caused by a mutation in the pax6 gene, which is vital for early eye development and has a key role in regulating limbal stem cell proliferation.(31) Aniridia results from a dysregulation in the communication between the developing corneal epithelium and the anterior compartment of the eye.(31) It is characterised by a progressive opacification of the cornea and the development of keratopathy.(31)

Secondary causes of LSCD often arise as a result of direct damage to the limbal stem cells.(25) This is most frequently associated with the sequelae of thermal (sometimes referred to as physical) or chemical (acid or alkali) burns and may also arise as a result of direct instilled drugs, contact lens usage or some therapies.(25) For example, the prolonged use of high dose topical mitomycin C application may be associated with a relatively high incidence of LSCD.(32)

Secondary causes of LSCD also arise as a result of systemic conditions such as SJS.(25) SJS is a multisystem inflammatory disorder that affects skin and mucous membranes, including the conjunctiva.(28) During SJS, inflammation of the OS is believed to stimulate the cell death of limbal stem cells and the development of LSCD.(28)

Idiopathic LSCD is rare and may be poorly recognised.(29) A 2002 study reviewed records from seven patients who had confirmed LSCD in whom the cause was never identified.(29) The patients were predominantly white, female and with similar symptoms of photophobia. There was a positive familial tendency, which suggested a possible, as yet unidentified, genetic influence.

### *3.1.2 Epidemiology of moderate to severe LSCD*

LSCD is an important cause of corneal blindness.(33) LSCD is most frequently seen associated with severe physical or chemical burns(24,25,28) and bilateral involvement is reported to affect 20-38% of patients presenting with chemical burns.(34,35) Chemical burns are typically caused by acid or alkali injury(28,35) with household cleaners containing sodium hydroxide being among the most common causes of alkali injury. Acidic injuries are less common than alkali injuries and typically cause less damage to the OS.(28)

The estimated prevalence of LSCD due to ocular burns in Europe is 0.3 per 10,000 people.(3) In the UK, the reported incidence of LSCD due to severe chemical corneal injury is 0.02 per 100,000 in patients who had a mean age at time of injury of 33.8 years (median 38.5 years, range 10-59 years).(36)

The most substantial evidence documenting the cause of LSCD comes from a 2011 review of 28 case reports and series published over 13 years.(37) Data from 583 patients (597 eyes) from centres undertaking cultured LSCT in Australia, Germany, India, Iran, Italy, Japan, Taiwan, UK, and USA was examined. In the studies reviewed, 75% of LSCD cases were caused by physical or chemical burns. In addition, the majority of patients were young males, treated for burns (Table 8).

**Table 8. Summary of causes of LSCD**(37)

| Cause of LSCD | Percentage of cases, % (number of eyes) |
|---|---|
| Physical or chemical burns | 75 (449) |
| Inflammatory eye disease (SJS and ocular cicatricial pemphigoid) | 7.8 (47) |
| Hereditary (Aniridia and ectodermal dysplasia) | 2.5% (15) |
| Other causes (recurrent pterygia and iatrogenic causes such as limbal surgery, mitomycin C treatment, and radiation therapy) | 14% (86) |

A 2015 study of 16 patients(38) also documented chemical burns (31%) as the most common cause of LSCD. Iatrogenic causes (25%), and aniridia (19%) were the next most frequent causes of LSCD. Aniridia is the most common cause of hereditary LSCD.(27)

Chronic effects on the ocular system have been documented in people exposed to sulphur mustard, (a chemical warfare agent) during the Iran-Iraq war, with an incidence of approximately 1%.(39) One of the fundamental chronic outcomes is LSCD. It is not clear whether LSCD is a direct effect of sulphur mustard toxicity or whether LSCD gradually progresses to a severe form because of chronic inflammation.(39)

### *3.1.3 Course of moderate to severe LSCD*

LSCD is a severe and painful condition that can affect patients with varying degrees of extent and severity.(10,38) It can be unilateral (affecting one eye) or bilateral (both eyes) and either partial or total (affecting part or all of the cornea).(10,38) Although partial LSCD may be limited to a few sectors of the cornea, central vision can still be compromised.(27) If the problem is bilateral, the patient may be effectively blind. Corneal blindness affects QoL and is often associated with an increased economic burden.(33)

In terms of health consequences for patients with LSCD, the associated OS disease poses a difficult management problem.(2) The clinical signs of LSCD are conjunctivalisation of the cornea with associated goblet cells, intense vascularisation, chronic inflammation, recurrent epithelial defects and stromal scarring.(10) Intense inflammation can cause secondary problems like increased eye pressure, the development of glaucoma and death of the optic nerve ganglion cells.(33)

From the patient's perspective, the eye has little or no vision, it is often cosmetically unsatisfactory, and it may be uncomfortable or painful.(2) The symptoms experienced include excessive pain, eye discomfort associated with OS problems including severe irritation, discomfort, photophobia, tearing, blepharospasm, chronic inflammation and redness, and decreased vision.(29,40) Most patients will lose their vision during the course of the disease.

### *3.1.4 Current management and unmet needs*

Physical and chemical burns have the potential to cause serious injuries. When the eye is involved, ocular burns can affect the limbus, cornea and conjunctiva (as well as deeper and adjacent structures) and can be particularly challenging to manage.(41) Patients with damaged limbal tissue may go on to develop LSCD and experience conjunctivalisation, corneal NV, corneal opacification and PEDs. All of these lead to decreased vision and ocular pain.(42)

The hierarchy of therapeutic options for LSCD varies from symptom control using conservative measures to surgical intervention involving the transplantation of viable epithelial 'stem' cells.(25,43) The goal of LSCD treatment is to restore the OS and corneal clarity.(41)

The primary measures of success in treatment for LSCD include the clinical presence of a stable OS, i.e. transparency, no superficial corneal vascularisation, no conjunctivalisation and no epithelial irregularity, defects or breakdown.(44,45) Improvement in vision is typically the secondary measure.(44) In addition, photophobia and pain can be used as outcome measures.(25)

Conservative therapeutic options include supportive management, corneal scraping, and AMT.(25) In partial LSCD, recovery depends on the presence of some remaining LESCs that can be rehabilitated to restore the epithelium.(25) In total LSCD, where there are no remaining stem cell reserves, the cornea may be reseeded with new LESCs using sections of donor tissue either from the patient's fellow eye (autograft, CLAU) or from a LRD or CD (allograft: CLAL, KLAL) in a procedure known as LSCT.(25)

Patient selection, counselling of recipients and potential donors, close postoperative monitoring, and multiple interventions (both medical and surgical) are key to the success of LSCT. Severe dry eye and chronic inflammation are important adverse factors. LSCT should be avoided in patients with the former, and the latter should be aggressively controlled before and after surgery.(46)

### *Supportive management*

Supportive management includes OS lubrication to prevent epithelial adhesion to the tarsal conjunctiva and reduce shear stress.(25) In addition to lubricating the OS, autologous serum drops also promote migration and proliferation of healthy epithelium. Therapeutic soft contact lenses may be used to promote healing of PED and prevent the formation of new defects.(25) Therapeutic scleral lenses also may improve vision and reduce pain and photophobia.(25)

### *Conservative surgical options*

#### *Corneal scraping*

Corneal scraping and AMT are conservative surgical options.(25) Corneal scraping aims to remove overgrown conjunctiva, to enable re-epithelialisation by islands of functioning corneal epithelial stem cells. However, because the conjunctival epithelium migrates more rapidly than the corneal epithelium, it may be necessary to repeat the procedure two to three times.(25)

#### *AMT*

The amniotic membrane is an immunologically inert, semi-transparent tissue from the inner part of the placenta.(47) An AMT promotes proliferation and migration of residual LESCs and a reduction of inflammatory reactions.(47) This promotes a healthy epithelium with reduced corneal NV(41) and contributes to the recovery of the corneal surface, improved VA, and alleviation of pain and photophobia.(25) An AMT may be performed immediately after corneal scraping as the overgrown conjunctiva is removed and the amnion membrane is patched over the epithelial defect.(25) However, variations in the biological source of the membrane may affect clinical outcomes(25) and there is a theoretical risk of disease transmission hence serological screening of the donor's blood for syphilis, human immunodeficiency virus, and hepatitis virus B and C should be conducted before use.(40)

The use of AMT is considered a useful adjunct to LSCT procedures in an attempt to promote healing and has been used alone or in combination with CLAU, CLAL and KLAL to aid OS reconstruction in patients with chronic chemical burns.(9,41,47,48)

### *Invasive surgical techniques*

*Limbal stem cell transplantation*

LSCT techniques can vary in the source of donor stem cells and also on the carrier tissue used for the transfer of the limbal stem cells. Carrier tissue is needed in limbal transplantation because it is not possible to transfer limbal stem cells alone.(49)

LSCT may be performed by CLAU, CLAL or KLAL procedures.(25) Both CLAU and CLAL use the conjunctiva as the carrier tissue but differ in their source of limbal stem cells: for CLAU an autologous graft derived from the patient's healthy eye is used, and in CLAL an allogeneic graft derived from a consenting LRD is used. Meanwhile, KLAL uses an allogeneic graft derived from a CD and uses cornea as the carrier tissue.(25)

Unilateral or partial LSCD can be treated by transplantation of autologous limbal stem cells from the healthy to the diseased eye. However, if bilateral LSCD occurs, the treatment relies on the transplantation of allogeneic limbal stem cells.(50)

Surgical treatment of bilateral LSCD is one of the most challenging tasks in OS disease management.(50) The success of LSCT may be evaluated by the epithelialisation of the cornea or clear graft survival and detection of donor-derived epithelial cells on the corneal surface.(51) CLAU, CLAL and KLAL can been associated with significant challenges that may prevent patients from undergoing these procedures.(37) These challenges include the need for large amounts of limbal tissue, which can risk inducing LSCD in the donor eye, and in cases of allogeneic tissue, the requirement of potent immune suppression that can pose the risk of life-threatening opportunistic infections and neoplasia.(37)

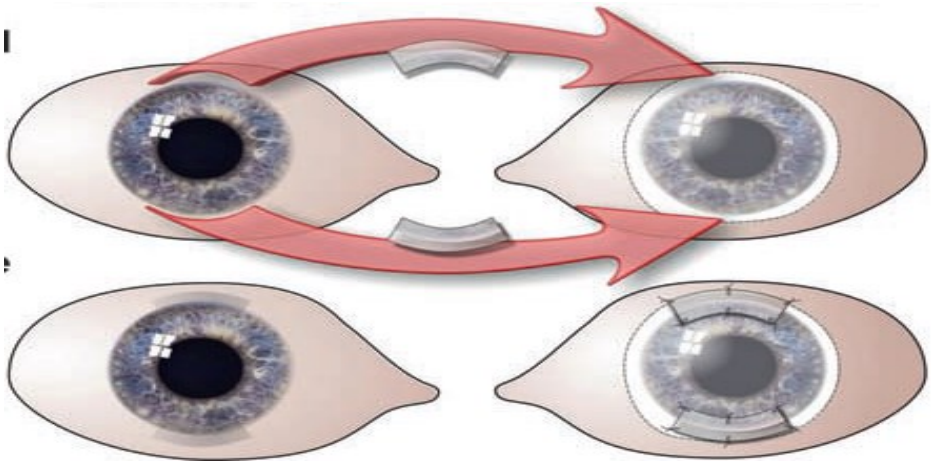
There is uncertainty regarding the best surgical management of LSCD.(9) The procedure choice may be based on several factors, including the presence of bilateral or unilateral disease, the extent of the LSCD, patient expectations and acceptance of the procedure, risk to a healthy eye, and the availability and willingness of a LRD.(40,52)

The risk of LSCT failure increases if the recipient has external eye diseases such as dry eye, eyelid or lid margin abnormalities, extensive conjunctival metaplasia, keratinisation, corneal anaesthesia, tear film abnormalities, mucus depletion, and chronic inflammation.(40)

*CLAU*

CLAU is considered an effective procedure for rehabilitation of eyes with unilateral partial or total LSCD.(53,54) As tissue is sourced from the patient's healthy eye, no systemic immunosuppression is required for this surgical intervention.(9) However, CLAU requires a large section of limbal tissue (between 2-3 clock hours, i.e. 4-6 $mm^2$ minimum) from both the superior and inferior portion of the limbus of the donor eye (8-12 $mm^2$ minimum total) for restoration of the OS.(44,55,56) Removing this amount of limbus from the donor eye introduces the risk of inducing LSCD in the healthy donor eye.(25,44) This may be an unacceptable risk for some patients, who may decline the procedure. Furthermore, if this procedure fails it cannot be repeated as the patient's healthy eye cannot be used again to donate conjunctivolimbal tissue.

**Figure 3: Illustration of the CLAU procedure**



In addition, the reported complications of this procedure include bleeding, viral/bacterial infection, inflammation, PED, corneal thinning, corneal melting, ulceration, perforation, glaucoma and recurrence of LSCD with progressive corneal conjunctivalisation.(25,54) Other complications that may occur are related to the transplanted limbal graft (size, thickness, position and alignment) and chronic OS

exposure.(54) Generally, complications after CLAU should be managed by prompt interventions.(54)

To achieve a long-term stable OS after CLAU a sufficient stem cell reserve in the treated eye is needed. It has been proposed that using two limbal grafts combined with AMT may be necessary to achieve this, although determination of the optimal size of limbal grafts needs further evidence.(54)

PK or DALK may be required for further visual rehabilitation. This is because stem cell deficiency may be accompanied by severe corneal stromal opacity and/or corneal endothelial dysfunction.(53,54)

Although, CLAU has been reported to be a very successful procedure, a drawback of it is that because of removal of fairly large segments of limbal tissue, the healthy donor eye is at risk of surgically-induced LSCD.(25,44) Despite this concern, reports regarding subsequent stem cell deficiency in a healthy donor eye are very rare and it seems that in the case of a good patient selection, it is a generally well-tolerated and uneventful procedure.(9) However patients may have reservations about using donor tissue from the only seeing fellow eye(42) and in cases where CLAU is unsuccessful, this procedure cannot be repeated and other treatment options must be used.

*CLAL*

In CLAL procedures, stem cells are taken either from a LRD or from a CD, thus effective immunosuppression is necessary to prevent immunological destruction of the transplanted limbal stem cells and allograft rejection.(49) Immunosuppression protocols vary but usually consist of a combination of topical and systemic agents. Common agents are prednisone, cyclosporine A, azathioprine, and dexamethasone.(40) Some protocols involve on-going immunosuppression while others taper and eliminate immunosuppression after 1 or 2 years.(40) Thus, systemic side effects associated with immunosuppression are a potential concern.(40)

The high risk of immunologic rejection compromises the success of the CLAL procedure.(50) Rejection may be endothelial or limbal: endothelial rejection results in

corneal opacification because of stromal oedema and limbal rejection is manifested by an unstable epithelial surface with recurrent erosions.(50)

Although an optimal HLA match is likely to improve outcomes,(50) HLA compatibility may not have any statistically significant effect on the survival of the graft.(42) It has been proposed that the underlying disease and severity of OS inflammation may be more predictive regarding survival.(50)

A disadvantage of CLAL is the limited amount of tissue that can be donated for transplantation (the procedure for LSC donation is essentially the same as that for CLAU except in a LRD rather than the patient's healthy eye). Therefore, in severe total LSCD, transplanted limbal stem cells may be unable to sustain sufficient long-term epithelial cell production for the entire limbus.(44) Another disadvantage is the possibility of induced stem cell deficiency in the donor.(25,44) CLAL also comes with an increased risk of transmitting infectious disease and promoting neoplasia due to the long-term use of immunosuppressants,(25) hence serological screening of the donor's blood for syphilis, human immunodeficiency virus, and hepatitis virus B and C is required before transplantation occurs. Furthermore, some surgeons in England do not offer lr-CLAL due to the high failure rate and potential compromise to the donor.(57)

*KLAL*

KLAL involves transplanting limbal stem cells taken from a cadaveric donor. This option is particularly suited to patients with total bilateral LSCD, especially when a LRD is unavailable.(9,46)

There is a need for a large section of the limbal tissue, approximately 6 clock hours (minimum 18 mm) for restoration of the OS.(25) However, an advantage of the KLAL procedure is that the entire CD limbus can be transplanted, and in practice a 360-degree lamellar ring that consists of the entire donor eye's limbus, most of the peripheral cornea and a minimal portion of the scleral tissue is used.(40) This maximises the number of transplanted stem cells without risking LSCD in the donor eye.(40) However, whilst in theory more limbal stem cells can be obtained from a CD than a live donor, the lengthy preservation time needed for HLA antigen matching results in limbal stem cell dropout.(58)

Although HLA matching is advisable it is almost impossible to obtain immune histocompatibility between the recipient and the donor cadaver.(40,42) Indeed, complete immunohistocompatibility between CD and recipients is rarely obtained,(58) hence systemic and topical immunosuppression is required. Furthermore, there is also evidence that LRD allografts fare better than CD allografts possibly due to the partial HLA matching between recipient and the LRD, as well as the increased expected viability of tissue retrieved from LRDs.(46)

A drawback of KLAL, however, is that it takes several weeks to achieve entire corneal surface epithelialisation from the CD graft, and in some cases, full epithelialisation may not occur.(59) There is also a theoretical risk of disease transmission,(25) hence serological screening of the donor's blood for syphilis, human immunodeficiency virus, and hepatitis virus B and C should be conducted before use. In addition formation of neoplasia secondary to immunosuppression may need to be considered.(25)

AEs including a reduction in VA from baseline and the development of glaucoma have been reported after KLAL.(9)

The risk of graft rejection after KLAL is high, because the limbal tissue is highly vascularised, highly antigenic and rich in Langerhans cells.(40,42) Thus, postoperative management, which includes immunosuppression, is very important in prolongation of graft survival. For success, KLAL with immunosuppression may need to be repeated more than once.(60)

Risk factors such as keratinisation, inflammation, and dry eye and symblepharon have been implicated for KLAL failure.(60,61) It is recommended that symblepharon should be surgically corrected prior to KLAL procedure.(60) Inflammation and postoperative infection may be triggered by use of sutures; they can be vascularised and may provoke graft rejection. The use of fibrin sealants instead of sutures in KLAL surgery may decrease the risk of rejection.(62)

*Adjunctive surgical procedures*

All the LSCT surgical options may be combined with PKP or DALK, with or without cataract surgery.(9) PKP and DALK are used to treat corneal stromal scarring that

may persist in patients with ocular burns even after the LSCD has been corrected. PKP involves a full-thickness corneal graft, whilst DALK is a less invasive procedure that selectively replaces the anterior layer of the cornea down to Descemet's membrane leaving the endothelium intact.

PKP used alone in LSCD offers temporary restoration of corneal transparency as eventually conjunctival cells begin to invade and resurface the cornea.(8)

The general health of the OS environment, with a good tear film layer and eyelid closure, is considered to be important for successful LSCT.(9) If there is severe associated dryness and scarring of the OS, keratoprosthesis (replacing a diseased cornea with an artificial cornea) is considered to be the only option.(9) The complications of a keratoprosthesis placement include infection, corneal melt, glaucoma, as well as formation of a retroprosthetic membrane.(41) A Boston type I keratoprosthesis is suitable for high risk patients for corneal transplantation, such as those with repeated graft failure or severe OS disease and has been used in managing bilateral LSCD secondary to ocular burns.(63,64)

**Table 9: Summary of comparator technologies**

| **Supportive treatment** | **Conservative surgery** | **Limbal stem cell transplantation** | |
|---|---|---|---|
| | | **Procedure** | **Features** |
| Autologous serum drops<br><br>Eye lubrication<br><br>Therapeutic soft contact lens<br><br>Therapeutic scleral lens | Corneal scraping<br><br>AMT | CLAU | Autograft from patient's healthy eye. Unsuitable for bilateral LSCD. No immunosuppression required. Minimum 4-6 $mm^2$ of limbal tissue superiorly and inferiorly (minimum 8-12 $mm^2$ total) is dissected from the patients other healthy eye and transplanted using a conjunctiva carrier.(44,55,56) Risk of inducing LSCD in donor eye.(25,44) |
| | | CLAL | Allograft from LRD or CD. Suitable for bilateral LSCD. Requires systemic immunosuppression.(49) Minimum 4-6 $mm^2$ of limbal tissue superiorly and inferiorly (minimum 8-12 $mm^2$ total) is |

| | | | |
|---|---|---|---|
| | | | dissected from the LDR donor eye and transplanted using a conjunctiva carrier. Risk of disease transmission and neoplasia.(25) Risk of inducing LSCD in LRD eye.(25,44) |
| | | KLAL | Allograft from CD. Suitable for bilateral LSCD.(9,46) Requires systemic immunosuppression. Entire CD limbus can be transplanted using the cornea as carrier tissue.(29) Risk of disease transmission and neoplasia.(25) Risk of inducing LSCD in LRD eye.(25,44) |

## *3.2 Effects on patients, carers/families and society of moderate to severe LSCD due to ocular burns*

Patients with moderate to severe LSCD and their family face serious social challenges. Directly and indirectly visual impairment interferes with many daily activities. In the case of adults, the possibilities for gainful employment are severely limited due to being unable to meet the greater visual demands in work situations, as is their participation in many other activities. To this is often added a loss of social status and self-esteem. The physical limitations and psychosocial implications of visual impairment cannot be measured in exact monetary terms. Nevertheless, it is clear that they diminish the quality of life not only for visually impaired persons, but for their families as well.(65)

The effect of LSCD on patients is further exemplified by patient testimonial. The following testimonials have been provided by patients matching the indication for Holoclar, i.e. adults with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns.

Testimonial 1(66)

*“I’ll never forget the moment the blob of plaster fell into my eye. I was plastering a ceiling, looking up at my work (no protective goggles, like a total muppet) when suddenly it happened. It was just a small dollop, but it stung like mad, so I rinsed it out with a bottle of water. Job done, back to work, or so I thought.*

*A few hours later I was in A & E, my eye was in agony and I couldn’t see a thing out of it. I was terrified. The doctors told me that a chemical called lime, one of the ingredients of plaster had been eating away at my cornea (the surface of my eye) all afternoon and the damage was severe. They said that the stem cells that live on the front of my eye and keep it clear had been damaged and that it was touch and go whether or not they would recover. They didn’t and the front of my eye scarred and turned white. For three years I was blind in that eye. It looked awful too and I lost all of my self-confidence. I was resigned to spending the rest of my life like that.”*

Following a successful limbal stem cell transplantation procedure, patient 1 describes the impact of treatment:

*“I could hardly believe it! I could see the top letter on the eye chart again! The graft had ‘taken’. What was even better was the way my eye looked. No longer did I have a strange looking eye although it was still a little bloodshot from the operation. Over the following month my vision got better and better eventually returning to 100%. The redness went away too and you couldn’t tell the difference between my two eyes! It was so fantastic being able to see again.”*

Testimonial 2(66)

Patient 2, who was 38 years old at the time of providing his testimonial, was attacked on his way home following a night out in Newcastle in 1994. On the bus home he overheard a heated argument between two men, which spilled into a fight. When he intervened to break up the scuffle, one of the men began squirting ammonia around the bus. Mr. Turnbull was hit in his right eye, causing unilateral LSCD.

*"As soon as the liquid hit me I was in agony. The pain was unbearable. I went to hospital and was in there for two weeks. When I was able to finally open my eye I had lost just about all of my sight in it. It was like looking through cracked Perspex. It had a devastating effect on me. I lost my job and couldn't ride my mountain bike or*

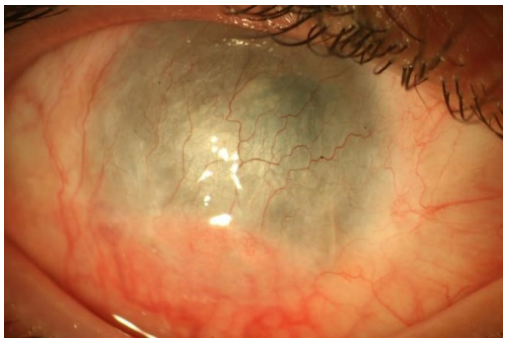
*go jet-skiing which I had enjoyed before. My eye was often in agony and would be weeping and red raw. If it was bad it meant I couldn't drive so it affected just about every aspect of my life. I had years of treatment but it was just trying different creams and ointments in a bid to stop the pain. None of them had any hope of restoring the sight."*

Following a successful limbal stem cell transplantation procedure, patient 2 describes the impact of treatment:(66)

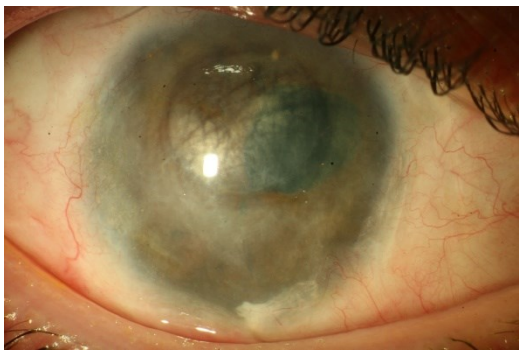
*"I never thought life would be this good again. I can never thank the doctors enough for restoring my sight. It's almost impossible to put into words what it means to me. I haven't just got my full sight back, I've got my life back. I'm working, I can go jet-skiing again and I also ride horses. I have my life back thanks to the operation."*

Despite the availability of the comparator technologies for many years prior to the Marketing Authorisation of Holoclar in 2015, there is a prevalent population of adult patients with moderate to severe LSCD, unilateral or bilateral, due to physical or chemical ocular burns for whom existing technologies have failed and unmet need exists. A pathognomonic case study featuring a patient with severe unilateral LSCD is shown in figure 4 below. This patient was initially treated with CLAU, which failed, and subsequently received treatment with Holoclar, which achieved a stable ocular surface without neovascularisation and improvement in visual acuity and allowed the patient to go on to receive a keratoplasty to address the deep stromal scarring associated with the initial injury.(67)

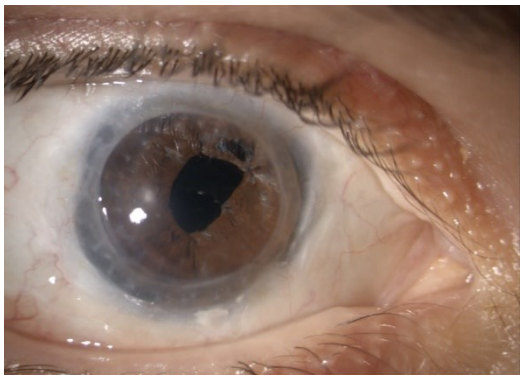
**Figure 4: Patient case study**(67)



Patient following treatment with CLAU



Patient following treatment with Holoclar

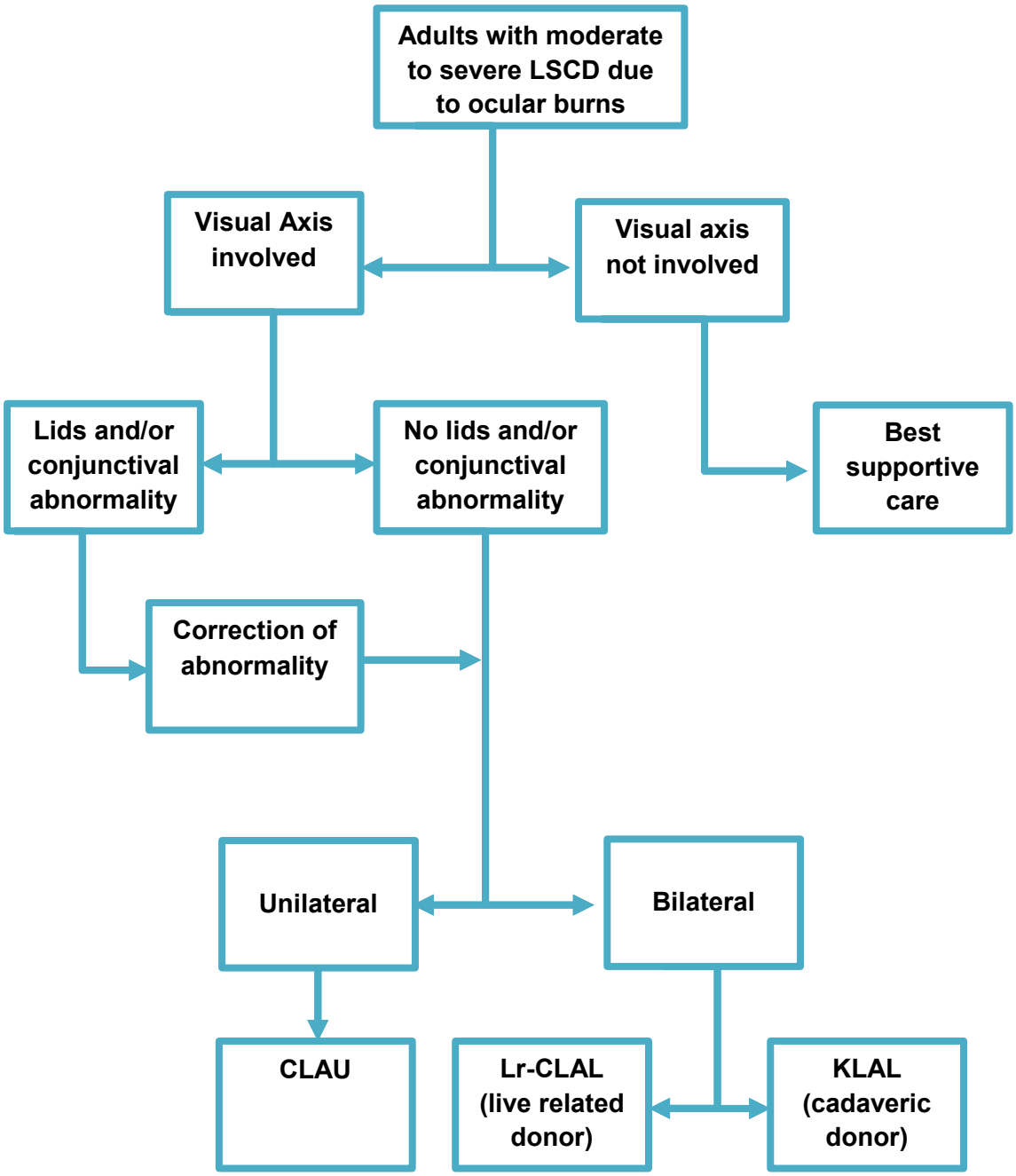


Patient following Holoclar + keratoplasty

## *3.3 Clinical pathway of care*

The current clinical pathway of care that shows the context of the proposed use of the technology is shown in figure 5 below:

**Figure 5: Context of the proposed use of Holoclar**




The proposed use of Holoclar in adults with moderate to severe LSCD, unilateral or bilateral, due to physical or chemical ocular burns is as follows:

- For unilateral LSCD, as an alternative to CLAU in patients who are unsuitable for CLAU or who are unwilling to undergo CLAU due to concerns about damage to their contralateral healthy donor eye or in whom CLAU has failed and cannot therefore be repeated.

- For bilateral LSCD where patients have a minimum of 1-2 $mm^2$ of undamaged limbus:

    - as an alternative to KLAL in patients who do not have an available and/or willing live-related donor;

    - as an alternative to lr-CLAL and KLAL in patients for whom topical and systemic immunosuppression is considered unsuitable or is undesirable; and/or

    - as an alternative to lr-CLAL and KLAL in patients who require the potential for a successful treatment outcome beyond 3-5 years.

The proposed introduction of Holoclar therefore does not alter the structure of the current clinical pathway within the NHS, but provides an alternative treatment option for the patient groups referred to above. This issue is further discussed in sections 3.5 and 3.6.

## *3.4 Life expectancy*

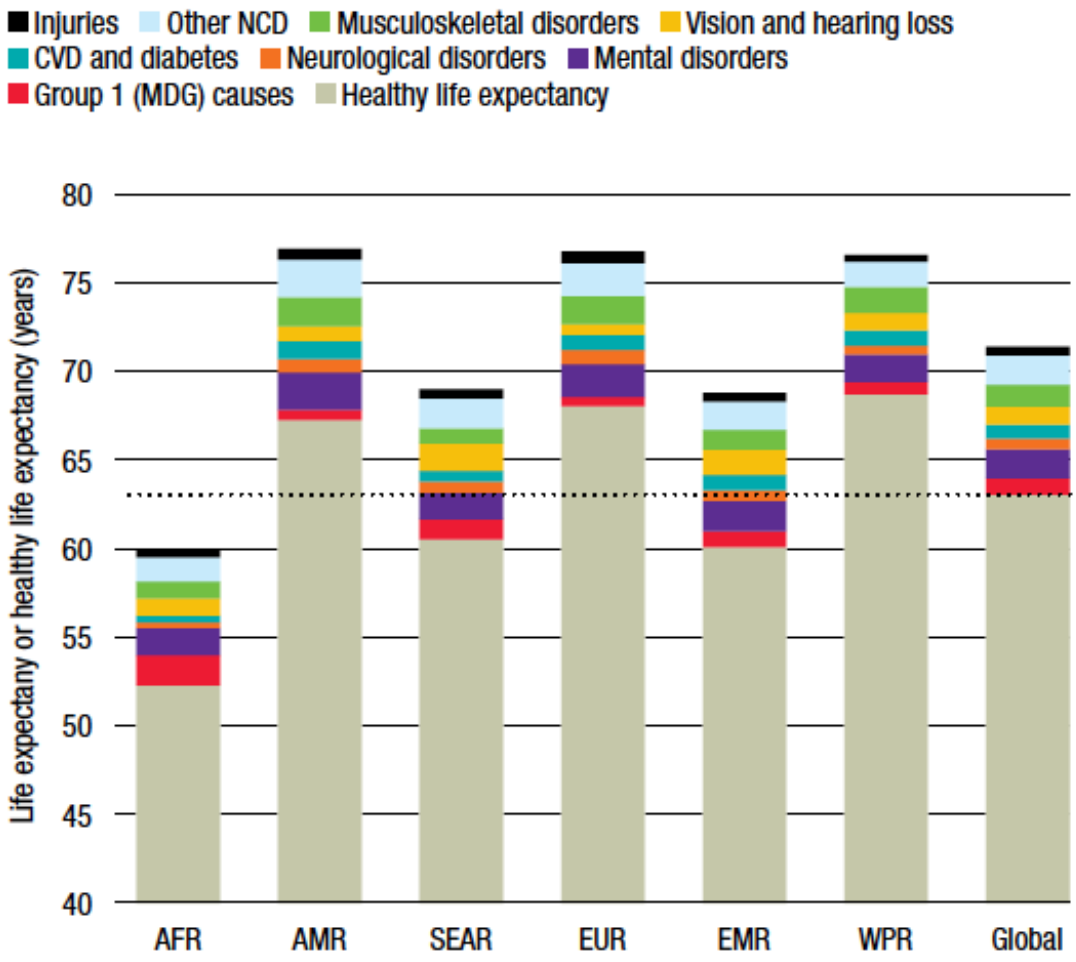
Given the estimated prevalence of LSCD due to ocular burns, 0.3 per 10,000 people in Europe,(3) there are no data examining the effects of this specific condition on life expectancy.

However, regional and global average life expectancies and health life expectancy at birth for 2015 have been reported by the WHO.(68) Healthy life expectancy provides an indication of overall health for a population, representing the average equivalent number of years of full health that a new-born could expect to live if they were to pass through life subject to the age-specific death rates and average age-specific levels of health states for a given period, and is considered an ideal indicator that captures both mortality and years of life lived in less than good health, i.e. in the case of a disability “years lost due to disability”.

In figure 6 below, the total height of the bar represents life expectancy at birth and the bottom part of the bar represents health life expectancy at birth. The gap between life expectancy and health life expectancy are the equivalent healthy years

lost through morbidity and disability. There are seven main contributors to the loss of healthy years, including vision loss.(68)

**Figure 6: Regional and global life expectancy and healthy life expectancy at birth, with cause decomposition of lost health expectancy, 2015**(68)




a Lost health expectancy is calculated as life expectancy minus healthy life expectancy. Horizontal dotted line indicates global health life expectancy.

### *3.4.1 Number of people affected*

LSCD due to ocular burns affects approximately 0.3 in 10,000 people in the European Union.(3) Therefore the estimated number of people with LSCD is 1,938 in the UK overall, based on population estimated from 2014 of 64.6 million.(69) Similarly, the estimated number of people with LSCD in England is 1,629.(69)

However, not all of these patients will be eligible to receive Holoclar as 24% of patients will be under 18 years of age,(69) reducing the number of adult patients to 1,238. Not all patients with ocular burns will be suitable for Holoclar. Market research conducted by Chiesi suggests that physical or chemical burns account for approximately 65% of all ocular trauma, equivalent to 805 patients.(70) Moderate to severe LSCD is associated with approximately 20% of physical or chemical burns, equivalent to 161 patients.(70) Of these, surgical cases account for approximately 75% of treatment type, equivalent to 121 patients.(70) Even then not all these patients will receive Holoclar, as patients with total bilateral LSCD (no undamaged limbus) cannot be biopsied or treated. This means that 121 patients will be the maximum estimated prevalent population for Holoclar. In addition to the prevalent population, the estimated incidence of new cases of severe chemical corneal injury in the UK is 0.02 in 100,000 people, i.e. 13 new cases per year.(36)

## *3.5 NICE guidance, pathways and commissioning guides*

For adults with moderate to severe LSCD, unilateral and bilateral, the alternative treatments to Holoclar that are currently funded/commissioned in the NHS are CLAU, CLAL and KLAL.

The related interventional procedures are:

- Corneal endothelial transplantation (2009) NICE interventional procedures guidance 304.(71)
- Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium' (2007) NICE interventional procedures guidance 216.(72)

Recommendation of Holoclar under a NICE single technology appraisal would provide an alternative treatment option to corneal endothelial transplantation as outlined in NICE IPG 304 in some patients with unilateral and partial bilateral LSCD.

Recommendation of Holoclar under a NICE single technology appraisal recommendation would provide a preferred treatment option to tissue cultured limbal stem cell allograft transplant for regrowth of corneal epithelium as outlined in NICE IPG 216 in appropriate patients.

The related NICE pathway is:

- Eye conditions (2015) NICE pathway.(73)

In the eye conditions pathway, it is proposed that Holoclar would fit within the 'Front of eye' section if recommended for use, under the subsection 'Other corneal disease'. As the pathway is poorly defined, and most current surgical treatment options which are currently in use have not been assessed by NICE; the introduction of Holoclar under a NICE single technology appraisal recommendation would provide some clear guidance in this part of the pathway.

## *3.6 Clinical guidelines and national policies*

For adults with moderate to severe LSCD, unilateral and bilateral, the relevant clinical guidelines and policies are:

- Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014.(74)

Recommendation of Holoclar under a NICE single technology appraisal recommendation would support the NHS in improving 'Domain 2 - Enhancing quality of life for people with long-term conditions', and specifically the overarching indicator number 2, 'Health-related quality of life for people with long-term conditions (ASCOF 1A**)'.

- NHS England (2014) Manual for prescribed specialised services 2013/14. Chapter 13. D12 - Adult specialist ophthalmology services.(75)

- NHS England (2013) NHS standard contract for specialised ophthalmology (adult). Schedule 2 - the services - A. The specifications.(76)

- NHS England (2013) 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults). Particulars, schedule 2- the services, a- service specification.(77)

NHS England is the responsible commissioner for specialised ophthalmology services, and the Manual for Prescribed Services states that the NHS CB (NHS England) commissions the following specialist services, including emergency care,

for corneal disorders (severe anterior segment inflammation, high risk keratoplasty, endothelial keratoplasty, keratoprosthesis, collagen cross linking, excimer laser to treat corneal pathology), as well as oculoplastic surgery.(75)

NHS England has stated that the responsibility for commissioning ex vivo expanded autologous human corneal epithelial cells (Holoclar) sits with NHS England (not CCGs).(75)

The NHS standard contract for specialised ophthalmology services, states that current commissioned treatments by NHS England include 'Ocular surface reconstruction- keratolimbal allografts, ex vivo stem cell allografts, cultured oral mucosal epithelial transplant, conjunctival limbal autograft (living related also).(76)

The NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults) is not expected to be impacted as it is not a direct comparator to ex vivo expanded autologous human corneal epithelial cells (Holoclar).(77) However, should improved success rates be seen in clinical practice compared with current treatment options, it is possible that the need for this intervention might be decreased from this patient group who may latterly be candidates for this treatment.

As such it is expected that a variation to the NHS specialised ophthalmology contract, or more likely the creation of a separate service specification and contract for ex vivo stem cell autografts will need to be created by NHS England to commission this service.

## *3.7 Issues relating to current clinical practice*

No transplantation procedure stands alone and, as for Holoclar, for a successful outcome of CLAU, CLAL and KLAL, it is essential that additional combination treatments are used and that appropriate pre-operative screening and post-operative follow-up take place. These additional requirements, and associated expenditure to the NHS, will not necessarily be reflected in the current cost codes for CLAU, CLAL and KLAL, yet are necessarily incurred. Expert opinion has been sought regarding the requirements for these in current clinical practice in England and suggests the following:

*CLAU*(56)

In addition to the CLAU procedure, the recipient eye requires the following:

- Amniotic membrane transplantation, either 2cm x 2cm or 2cm x 4cm depending on the size of the recipient eye.
- Autologous serum eye drops for a period of 3 months (at a cost of £1,700 per batch that last for 60 days).
- Tarsorrhaphy (with subsequent reversal procedure to follow).
- Systemic steroid, e.g. prednisolone 60 mg daily, with omeprazole cover. The dose of prednisolone is tapered after 1 week and discontinued after 2 weeks.
- Topical steroid eye drops.
- Topical antibiotic eye drops.
- Lubricant eye drops.

The donor eye requires the following additional treatment:

- Bandage contact lens (changed every 8 weeks until healing has occurred).
- Antibiotic eye drops for 2-4 weeks.
- Topical steroid eye drops for 2-4 weeks.
- Lubricant eye drops.

The schedule for outpatient review following CLAU is as follows and all clinic visits take place in tertiary care:

- Routine follow-up appointment at 1 week.
- Reversal of tarsorrhaphy at 14 days post-operative (assuming no complications requiring this to be postponed).

- Review every 4 weeks until a stable, intact epithelium is obtained (usually at 3 months post-op).

- Once the epithelium is stable, review 1-2 monthly up to a year whilst weaning and stopping antibiotic and steroid eye drops.

- At approximately 1 year post-operative review in clinic to determine if corneal keratoplasty is required. If keratoplasty is required, then undertake the procedure. If keratoplasty is not required, patients continue to be reviewed in clinic annually.

*Lr-CLAL*(56)

Essentially, this follows the same procedure as for CLAU above, with the difference being that the donor eye is from a live relative. Consequently clinical practice differs as follows:

- Two sets of pre-operative assessments and 2 sets, which incurs additional clinic time and resource.

- Two sets of post-operative appointments are required, which incurs additional clinic time and resource.

- Tissue typing is not routinely undertaken, but HLA matching is required.

- Viral and syphilis screens are required to be performed in the donor.

- Typically the donor would be followed up for the first 4-8 weeks (as per previous schedule for CLAU) with an additional follow-up appointment at 6 months to check that the harvesting procedure has not caused LSCD or any other long-term sequelae in the donor eye. AEs in the donor are unlikely, assuming compliance with bandage contact lens and steroid/antibiotic/lubricant drops). The aim is to discharge the donor at 6 months post-op.

- Recipients are managed as per previous schedule for CLAU except where HLA matching is poor or there is HLA mismatch, in which case systemic

immunosuppression with mycophenolate is added. This requires assessment of baseline renal/hepatic function and subsequent renal/hepatic monitoring whilst on therapy. Mycophenolate is required at a dose is 1g twice daily and treatment continues until the graft fails.

*KLAL*(56)

Essentially, this follows the same procedure as for live related donor, except the donor eye is from a cadaver. The management differences are as follows:

- The recipient also requires additional post-operative immunosuppression with sirolimus plus rapamycin. This requires assessment of baseline renal function and subsequent renal monitoring whilst on therapy. Treatment continues until the graft fails.

## *3.8 Equality issues*

The Armed Forces Covenant is an agreement between the Armed Forces community, the Nation and the Government.(5) It encapsulates the moral obligation to those who serve, have served, their families and the bereaved. The covenant's twin underlying principles are that members of the armed forces community should face no disadvantage compared to other citizens in the provision of public and commercial services; and that special consideration is appropriate in some cases, especially for those who have given the most such as the injured or the bereaved.

Whilst for serving personnel, primary healthcare is provided by the Ministry of Defence and secondary care by local healthcare providers, veterans receive their healthcare from the NHS and should receive priority treatment where it relates to a condition that results from their service in the Armed Forces, subject to clinical need. Those injured in Service should be cared for in a way that reflects the Nation's moral obligation to them whilst respecting their individual's wishes.(5)

For Armed Forces personnel who acquire moderate to severe LSCD due to physical or chemical ocular burns sustained during service, e.g. due to explosive devices, the impact of LSCD in this group (unilaterally or bilaterally) may be further complicated by concomitant loss of limb and other life-threatening or life-changing injuries. As

such, this group is disproportionately affected by physical disabilities, and other mental health sequelae, which differ to the general population of patients with moderate to severe LSCD due to physical or chemical ocular burns.

The impact of LSCD and associated symptoms, including visual loss (which is commonly bilateral in patients with physical ocular burns), in patients with other life-changing disabilities, both physical and mental, means that the benefits of Holoclar might not be fully captured in the QALY calculation in this population. Indeed sudden painful loss of vision is expected to be prejudicial to rehabilitation from other disabilities. It is therefore likely that the return of sight, or improvement of visual acuity, would have more of an impact in patients with other simultaneously acquired physical disabilities that also restrict their ability to self-care and lead as normal a life as possible.

To fail to make Holoclar available via the NHS in England, especially for patients with bilateral moderate to severe LSCD due to ocular burns where Holoclar is dominant to lr-CLAL and KLAL, would therefore raise a significant equality issue given the disproportionate compromise this would cause to concomitantly disabled Armed Forces veterans. Furthermore, failure to provide the best available clinical outcomes and the opportunity for long-term visual rehabilitation (and without the need of immunosuppression) in these patients is prejudicial to the rehabilitation of other disabilities sustained during service in the Armed Forces, a rehabilitation process that is already provided and funded by the NHS. This is also fundamentally contrary to the Armed Forces Covenant the moral obligation that the Government and the Nation have to those who serve.(5)

# 4 Clinical effectiveness

## *4.1 Identification and selection of relevant studies*

A systematic literature search was conducted to identify and select relevant studies examining the clinical effectiveness, safety and impact on HRQoL of Holoclar and comparator technologies. In line with standard methodology, multiple databases were used:

- Embase
- Medline (through PubMed)
- Cochrane Library:
    a. Cochrane Database of Systematic Reviews (Cochrane reviews)
    b. Database of Abstracts of Reviews of Effects (Other reviews)
    c. Cochrane Central Register of Controlled Trials (Clinical trials)
    d. Cochrane Methodology Register (Methods studies)

In order to identify relevant findings presented at international scientific conferences during the past 2 years that may not yet have been published in MEDLINE or EMBASE indexed peer-reviewed journals, the following “grey” literature sources (material that can be referenced, but is not necessarily published in peer-reviewed, MEDLINE or EMBASE indexed medical journals) were also manually searched for any relevant information. All of these sources are international scientific conferences:

- American Academy of Ophthalmology (AAO)
- European Association for Vision and Eye Research (EVER)
- European Society of Ophthalmology (ESO)
- Investigative ophthalmology & visual science (IOVS)
- The Royal College Of Ophthalmologists (RCO) Annual Congress

- World Congress of Ophthalmology (WCO)

The literature search included studies of human subjects published in English and non-English. The period covered by the literature search was January 1989 to January 2016 for published papers and January 2014 to January 2016 for conference material. Full details of the search strategies and search terms used are provided in the systematic review report for Holoclar, see Appendix 4.

Given that LSCD is a rare condition(3) and, prior to Holoclar, no medical therapies have been available to treat this condition, it was expected that only a small number of studies would likely be identified. Therefore, the inclusion criteria were simplified to take this into account. The inclusion and exclusion criteria are set out below:

Inclusion criteria:

- Published in English and non-English
- Human population
- Patients with a confirmed diagnosis of LSCD

Exclusion criteria:

- Outside of scope, i.e. did not address efficacy or safety of CLAU, CLAL, KLAL or Holoclar
- Studies that were conducted in paediatric patients (aged <18 years)
- No clinical data presented for CLAU, CLAL, KLAL or Holoclar
- Inadequate detail of data

One further paper (sourced from EMBASE) was excluded because it was not published or otherwise listed on the journal website and therefore appears to have been indexed in error in EMBASE.

Two reviewers independently inspected each reference (title and abstract) identified by the literature search and applied the study selection criteria. For possibly relevant articles (i.e. where relevance is not clear), or in cases of disagreement between the

two reviewers, the full article was obtained and inspected. Secondary assessment outlining the reasons for reference exclusion was provided.

PRISMA flow diagrams showing the numbers of studies included and excluded at each stage is provided below:

**Figure 7: PRISMA flow diagram of evidence for clinical effectiveness, safety and impact on HRQOL for Holoclar in the treatment of moderate to severe LSCD due to physical or chemical ocular burns**

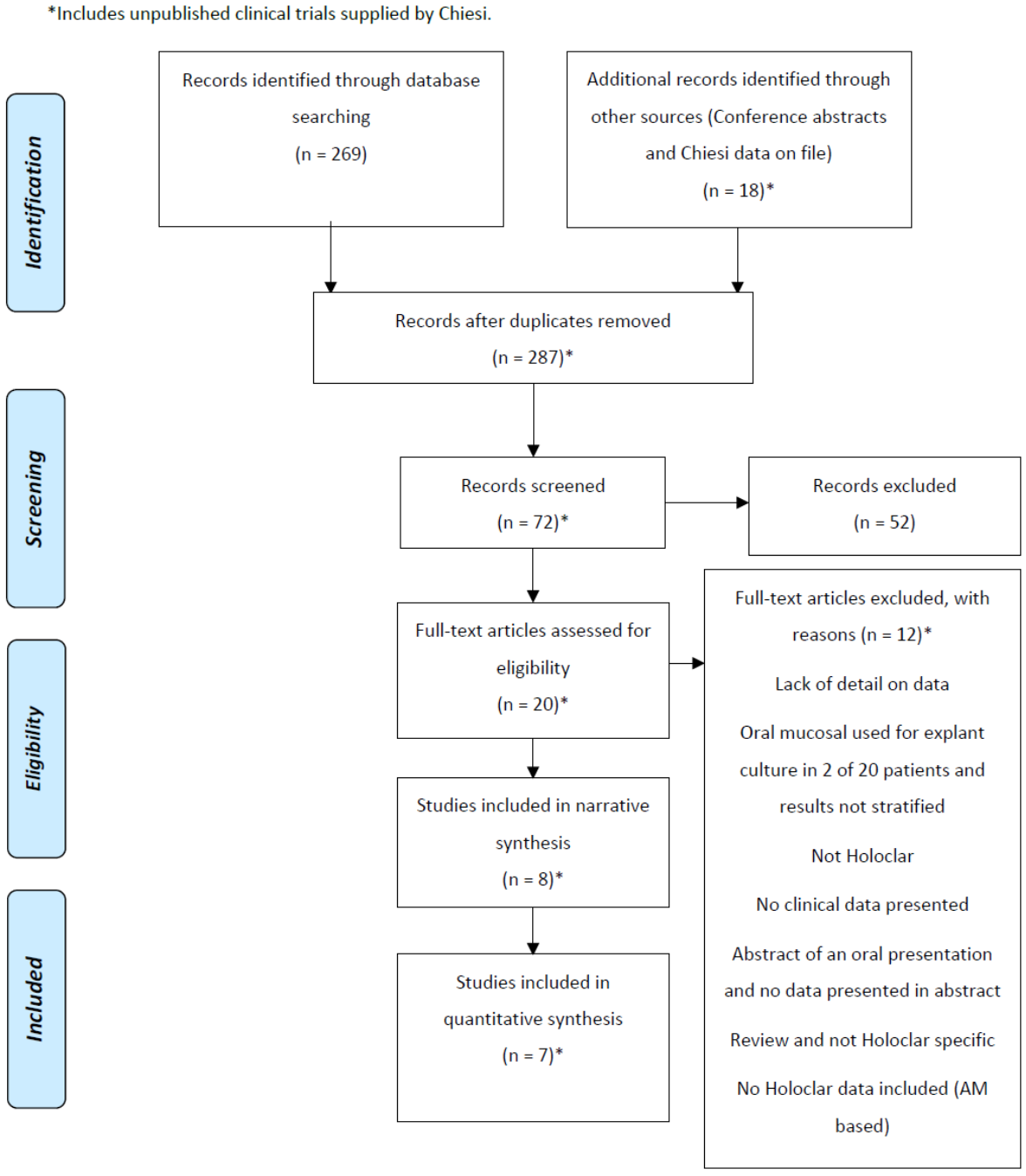
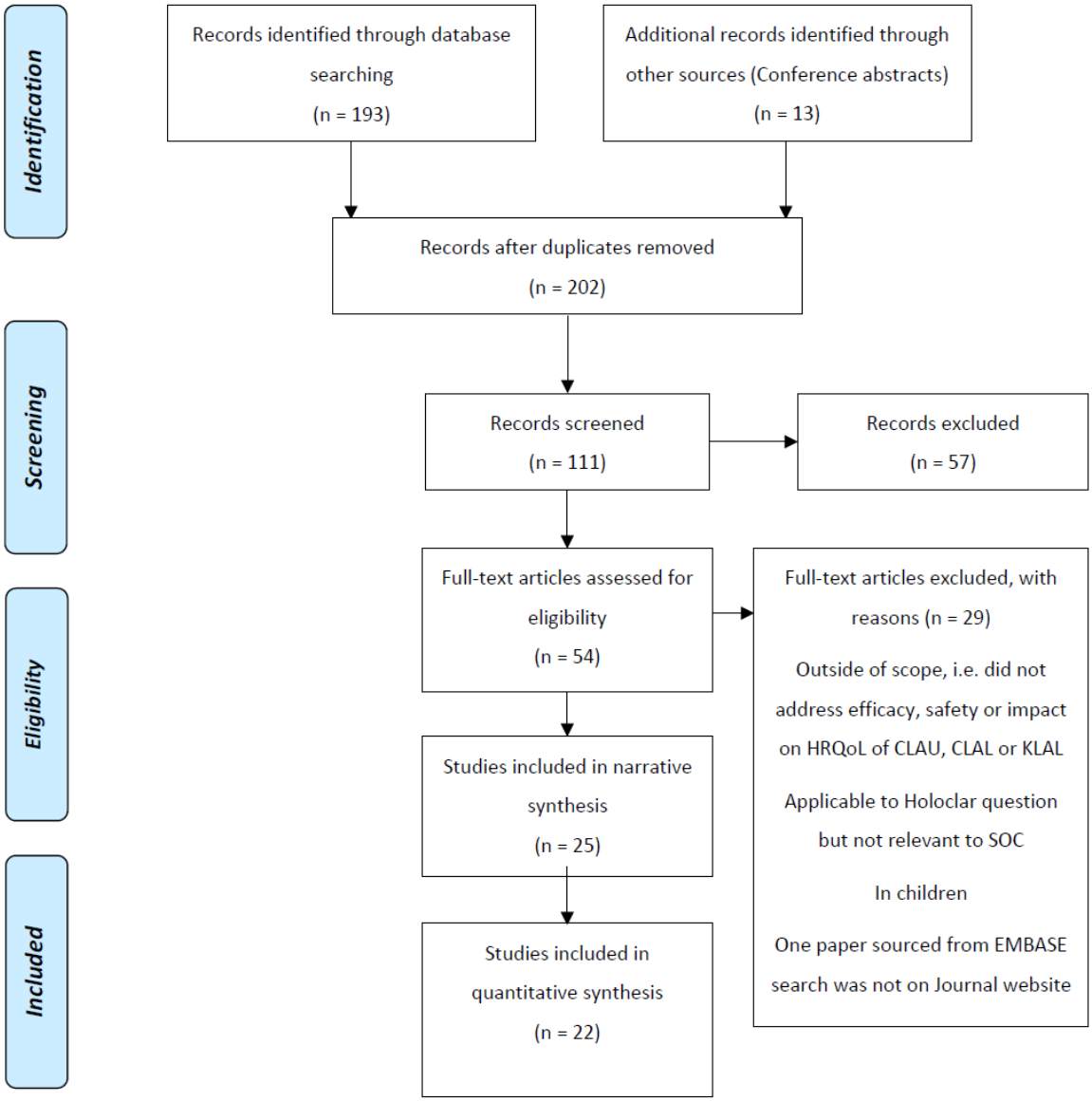


**Figure 8: PRISMA flow diagram of evidence for clinical effectiveness, safety and impact on HRQOL for comparator technologies in the treatment of moderate to severe LSCD due to physical or chemical ocular burns**




A complete reference list for excluded studies with the reason for their exclusion is provided in the systematic review report for Holoclar, see Appendix 4.

## *4.2 List of relevant randomised controlled trials*

There are no randomised controlled trials that provide evidence on the clinical benefits of Holoclar, or the comparator technologies conjunctival limbal autograft, limbal epithelial stem cell allografts and best supportive care, for the treatment of

adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns.

That there are no randomised controlled trials conducted in this patient group and indication is entirely to be expected for the following combined reasons of ethics and feasibility:

- Although patients with unilateral LSCD can (in theory) be treated with LSC allografts, this is not a recommended first-line approach in these patients due to the requirements for immunosuppression and the likelihood of these procedures, where they do succeed, to achieve only a temporary success. It would therefore be considered unethical to risk randomly allocating patients with unilateral LSCD to receive a LSC allograft in the first instance.

- Patients with unilateral LSCD are not always willing to accept CLAU due to the potential risks to their remaining unaffected 'donor' eye. It would therefore be considered unethical to risk randomly allocating patients with unilateral LSCD to receive CLAU against their wishes.

- Patients with LSCD do not always have an available and willing live related donor who would be prepared to donate limbal stem cell tissue (with the associated potential risks to their own donor eye) were a patient with unilateral or bilateral LSCD to be randomly allocated to receive a LSC allograft from a live related donor. It is therefore both unethical and unfeasible to design a trial that randomly allocated patients to receive a LSC allograft from a live related donor.

- As surgical intervention is considered superior to BSC, it would be considered unethical to withhold LSC transplantation from a patient with LSCD by risking random allocation to receive best supportive care alone.

- Blinding/masking of treatment allocation both for the surgeon and the patient is unfeasible. For CLAU, patients require two surgical procedures to be undertaken on the same day; one procedure for donation of LSC tissue from

the healthy donor eye, immediately followed by a second surgical procedure to transplant the healthy LSC tissue to their affected eye. Patients receiving a LSC allograft from a live related donor, who is usually a close family member, will likely be aware of the surgical donation procedure conducted on one of their eyes of their relative and not on one of their own eyes. Patients receiving a LSC allograft from a cadaveric donor will likely be aware of no donor procedure being conducted either on one of their own eyes or on the eye of a relative. For Holoclar, patients will be aware of the initial biopsy procedure performed on one of their eyes followed by the implantation of Holoclar a few weeks later. Consequently, a combination of the donor source (patient/relative/ neither) and the timeline required between biopsy and implantation for Holoclar will undermine any attempt at conducting a blinded/masked study.

- Finally, the estimated prevalence of LSCD due to ocular burns is 0.3 in 10,000 people in Europe.(3) Consequently, there are insufficient patients with LSCD due to ocular burns to conduct randomised controlled trials of Holoclar vs. conjunctival limbal autograft, limbal epithelial stem cells allografts and/or best supportive care.

## *4.3 Summary of methodology of the relevant randomised controlled trials*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.5 Participant flow in the relevant randomised controlled trials*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.6 Quality assessment of the relevant randomised controlled trials*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.7 Clinical effectiveness results of the relevant randomised controlled trials*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.8 Subgroup analysis*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.9 Meta-analysis*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.10 Indirect and mixed treatment comparisons*

Not applicable as there have been no published RCTs in the treatment of moderate to severe LSCD due to ocular burns.

## *4.11 Non-randomised and non-controlled evidence*

There are no studies directly comparing Holoclar with any of the comparator technologies. All published evidence for the treatment of adults with moderate to severe LSCD due to physical or chemical ocular burns both for Holoclar and the comparator technologies is almost exclusively based on non-randomised, non-controlled, non-comparative case series.

### 4.11.1 Relevant non-randomised and non-controlled evidence

For Holoclar, 8 studies were identified by systematic literature search as relevant for inclusion in this technology appraisal, including 3 unpublished studies provided by Chiesi. These 8 studies are described in tables 10 and 11 below. Of these, 7 studies

provided data relevant to the outcome measures identified in the scope and are subsequently discussed in relation to the clinical effectiveness results for Holoclar.

For the comparator technologies, 25 studies were identified the systematic literature search as relevant for inclusion in this technology appraisal. These 25 studies are described in table 12 below. Of these, 22 studies provided data relevant to the outcome measures identified in the scope and are subsequently discussed in relation to the clinical effectiveness results for the comparator technologies.

**Table 10: Published studies of Holoclar identified by the systematic literature search**

| Author, *Journal*, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Marchini, Clin Experiment Ophthalmol 2012 (78) | Italy, prospective, non-comparative interventional case series in patients with severe unilateral LSCD, 12-50 months | Ex vivo cultured ACLSCT (n=16) | Clinical parameters of LSCD (stability/transparency of the corneal epithelium, superficial corneal vascularisation and pain/photophobia), VA, cytokeratin expression on impression cytology specimens and histology on excised corneal buttons | 12-50 months | Evaluation of the 16 patients showed that 10 (62.6%) experienced complete restoration of a stable and clear epithelium and 3 (18.7%) had partially successful outcomes (re-appearance of conjunctiva in some sectors of the cornea and instable corneal surface). Graft failure (no change in corneal surface conditions) was seen in three (18.7%) patients. |
| Pellegrini, Lancet 1997 (79) | Italy, proof of concept in unilateral severe LSCD due to chemical burns, >2 years | Ex vivo cultured ACLSCT (n=2) | Restoration of the corneal surface and long-term stability, symptoms and VA | >2 years | In the first patient, 2 weeks after grafting of cultures, the cornea was covered with a transparent normal-looking epithelium and fluorescein revealed minimal punctate staining. BCVA was 0.7 in the first patient, who had previously only been able to see hand movements. PKP was performed in this patient.<br>The second patient had one previously failed autograft and two failed allografts. |

**Table 10: Published studies of Holoclar identified by the systematic literature search**

| Author, *Journal*, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| | | | | | At admission, there was severe vascularisation, persistent ulceration, tremendous discomfort, stromal melting, and hardly any vision.<br><br>After the grafting of cultured epithelium, there was reconstitution of a stable and transparent corneal epithelium, absence of vascularisation with negative fluorescein staining and improvement in comfort were identical to those obtained in patient 1. Vision improved from near blindness to counting fingers at 1 metre.<br><br>Both patients were clinically stable after >2 years. |
| Pellegrini, Regen Med 2013 (80) | Italy, long-term multicentre prospective study in total unilateral LSCD due to ocular burns | Ex vivo cultured ACLSCT (n=152) | Full success (all symptoms had disappeared and a transparent, avascular and stable corneal surface had been restored), partial success (most symptoms | 8 years (5.10-14.5 years) | Full success, partial success and failure was achieved in 66%, 19% and 15% of eyes, respectively.<br><br>Because of stromal scarring, the treatment did not significantly improve |

**Table 10: Published studies of Holoclar identified by the systematic literature search**

| Author, *Journal*, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| | (n=144; 94.7%) and other causes (n=8; 5.3%) | | had disappeared but superficial NV had occurred, even if only sectorial) and failure (persistence of symptoms, recurrent epithelial defects, pannus and inflammation)<br>VA<br>Safety | | patients' mean ± SD VA (from 0.05 ± 0.09 [median: 0.02] to 0.15 ± 0.22 [median: 0.02]). In 56 patients who received DALK after grafting, VA improved from 0.02 to 0.60.<br>No AEs related to the feeder layer have been observed and the regenerated epithelium was completely devoid of any 3T3-J2 contamination. |
| Rama, Transplantation 2001 (81) | Italy, multicentre study in a homogeneous patient population with total (n=15) or severe (n=3) unilateral LSCD due to chemical burns, 12-27 months | Ex vivo cultured ACLSCT (n=18) | Restoration of the corneal surface and long-term stability, symptoms, VA | 12-27 months | Fibrin-cultured limbal stem cells were successful in 14/18 patients (78%). Re-epithelialisation occurred within the first week. Inflammation and vascularisation regressed within the first 3-4 weeks. By the first month, the corneal surface was covered by a transparent, normal-looking epithelium. At 12-27 months follow-up, corneal surfaces were clinically and cytologically stable. All patients reported a stable improvement of their symptoms: |

**Table 10: Published studies of Holoclar identified by the systematic literature search**

| Author, *Journal*, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| | | | | | burning, pain and photophobia. Three patients had PKP approximately 1 year after restoration of their corneal surface. In the successful grafts, the VA improved from light perception or counting fingers to VA ≥0.2 in 7/14 patients (50%) and VA ≥0.1 in 10/14 (71%). |
| Rama, N Engl J Med 2010 (8) | Italy, retrospective analysis of patients with severe or total, unilateral or partial LSCD due to ocular burns, 9 years | Ex vivo cultured ACLSCT (n=112 patients; 113 eyes) | Successful: Resolution of symptoms and restoration of a transparent, avascular and stable corneal surface as assessed by investigator<br>Partially successful: symptoms had disappeared but superficial NV had recurred, even if it was not as extensive as at the time of admission<br>Failure: presence of symptoms, recurrent | 10 years | **First graft:**<br>Success (n=number of eyes): n=73 (68.2%)<br>Partial success: n=18 (16.8%)<br>Failure: n=16 (15.0%)<br>**Second graft:**<br>Success: n=9 (75.0%)<br>Partial success: n=2 (16.7%)<br>Failure: n=1 (8.3%)<br>Final outcome: |

**Table 10: Published studies of Holoclar identified by the systematic literature search**

| Author, *Journal*, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| | | | epithelial defects, pannus, and inflammation at 1 year | | Success: n=82 (76.6%)<br>Partial success: n=14 (13.1%)<br>Failure: n=11 (10.3%)<br>After grafting, 46 patients underwent PKP (89%), DALK (9%) or phototherapeutic keratectomy (2%) to replace the damaged stroma.<br>Before this study, BCVA was <0.1 (i.e. light perception, hand movement and counting fingers) in 88.5% of the patients and was 0.1-0.5 in 11.5% of the patients. After grafting and corrective surgical procedures (n=46), permanent recovery of VA ≥0.6 (range, 0.6 to 1.0) was attained in 21 patients and VA up to 0.5 in the remaining 25 patients. Overall, in the patients with successfully or partially successfully grafts (n=96), 58 achieved a VA ≥0.2 (60%). |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| Chiesi Farmaceutici S.p.A., HLSTM01 2012 (7) | Italy, non-randomised, uncontrolled trial in patients with moderate to severe unilateral or bilateral LSCD due to ocular burns | Ex vivo cultured ACLSCT (n=104) | Success based on: superficial corneal NV as 'none' or 'mild'; epithelial defects classified as 'none' (no staining) or 'tracing' (minimum staining) | Change in symptoms (pain, burning, photophobia), inflammation and VA. Number of ACLSCTs in each patient. Number of successful keratoplasties after ACLSCT. Evaluation of impression cytology: percentage of K3+, K3-, K12+, K12-, K19+, and K19- cells, and presence of | 12 months | In the ITT group, 75 patients (72.1%) reported successful treatment (95% CI 62.5-80.5%). In the on-treatment (ITT sensitivity analysis) analysis, success occurred in 75 patients (75.8%, 95% CI 66.1-83.8%) and failure in 24 patients (24.2%). A total of 76 patients in the ITT group (73.1%) had an improvement from moderate or severe corneal NV to 'none' or 'mild' at 12 months | The number of patients with ocular symptoms significantly reduced ($p<0.001$) from baseline to 12 months post-transplantation. The number of patients with evidence of inflammation did not change from prior to treatment (32 patients; 30.8%; 95% CI 21.9-9.6%) to 12 months post-treatment (33 patients; 31.7%; 95% CI 22.8-40.7%). For superficial corneal NV based on photographic evidence evaluated by independent assessor: the proportion of patients |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | caliciform cells | | | decreased significantly (p<0.001) from baseline (93.8%; 95% CI: 88.6-99.1%) to 12 months after treatment. VA improved in 51 patients (49%; 95% CI 39.4-58.6%). Of the 57 patients undergoing keratoplasty, 24 patients (42.1%) had ≥1 successful keratoplasty post-treatment. Mean percentage of K3+ cells increased from 14.0% pre-treatment to 57.0% post-treatment. The mean percentage of K19+ cells decreased from 73.2% pre- |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | | | | treatment to 20.4% post-treatment.<br><br>A total of 194 AEs were reported in a total of 73 transplantation procedures (64.6%) over a follow-up period of 36.8 ± 23.0 months (range 1.05-118.5).<br><br>Overall, 6 serious AEs (3 were fatal) were reported after 6 transplantation procedures (5.3%), all in subjects with one transplantation (5.9%). None of them was considered as treatment-related.<br><br>A total of 22 ADRs were |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | | | | reported after 19 transplantation procedures<br>(16.8%).<br>There were no ADRs potentially related to antibiotics up to one month after transplantation. AEs potentially related to corticosteroids (occurring up to 3 months after transplantation) were reported in 6 cases (5.3%), 5 consisted of glaucoma and 1 of gastritis. Only one case of glaucoma was considered by the |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | | | | investigator as treatment-related (i.e. as ADR). |
| Chiesi Farmaceutici S.p.A., HLSTM02 2012 (82) | Italy, non-randomised, uncontrolled in patients with moderate to severe unilateral or bilateral LSCD due to ocular burns | Ex vivo cultured ACLSCT (n=29) | Number of subjects experiencing AEs and the number of AEs | Rate of ASCLCT recorded as success or failure based on investigator's judgement. Number of ASLSCTs in each patient. Number of successful keratoplasties after transplantation | ≥1 year | A total of 46 AEs were reported in 19 treatments (65.5%). Of these, 21 events occurring in 10 treatments (34.5%) were judged as ADRs. Eye disorders were the most common group of AEs observed, with eye pain (17.2%) and glaucoma (13.8%) as the most common single AEs reported. Corneal graft (keratoplasty) rejection was reported in 2 cases (6.9%). Another patient | A successful outcome was reported in 19 of 29 patients (65.5%; 95% CI 48.2-82.8), treatment failures were reported for six patients (20.7%). Six patients underwent at least one keratoplasty following treatment, with 4 successful outcomes reported (66.7%). |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | | | had other graft complications. One case of corneal infection after transplantation was reported. Five SAEs were reported in 3 treatments (10.3%) and 10 AEs of severe intensity were reported in 6 treatments (20.7%). Three SAEs in 2 patients were considered treatment-induced: vasovagal syncope in 1 patient, and ulcerative keratitis and corneal perforation in the other. None of the AEs led to study | |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | | | withdrawal | |
| Chiesi Farmaceutici S.p.A., HLSTM04 2014 (83) | Italy, non-randomised, uncontrolled in patients with moderate to severe unilateral or bilateral LSCD due to ocular burns | Ex vivo cultured ACLSCT (n=15) | Safety and efficacy of ACLSCT in restoring normal and corneal epithelium | Safety of ACLSCT, including biopsy, surgical procedure and post-surgical treatments in terms of AEs, SAEs, ADRs and serious ADRs | ≥3 months | 60% of ACLSCT were reported as successful at the last post-transplantation visit. Superficial corneal NV: before ACLSCT, 80% of patients with 4 quadrants and 20% patients with 3 quadrants involved at the pre-surgical visit; after ACLSCT, 67% patients without superficial corneal NV or only 1 quadrant involved at the last post-transplantation visit. Degree of corneal | 60% of patients experienced AEs (14 AEs), the most frequent being eye disorders and nervous systems disorders. Only one SAE was reported and characterised as not related to the procedure (stroke). |

**Table 11: Unpublished studies of Holoclar provided by Chiesi and identified by the systematic literature search**

| Author, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Secondary outcomes | Duration of follow-up | Primary outcome results | Secondary outcome results |
|---|---|---|---|---|---|---|---|
| | | | | | | epithelium integrity before ACLSCT, 40% patients without defects at the pre-surgical visit; after ACLSCT, 73% patients without defects at the post-transplantation visit | |

## Table 12: Published studies of comparator technologies identified by the systematic literature search

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| **Conservative non-surgical options (best supportive care)** | | | | | |
| Fernandes, Indian J Ophthalmol 2004 (84) | N/A | Therapeutic soft contact lens | N/A | N/A | A bandage contact lens may be used postoperatively and is usually applied to prevent dislodging of donor tissue by the shearing action of the lids, and to avoid injury to the growing epithelial edge. |
| Fernandes, Indian J Ophthalmol 2004 (84) | N/A | Eye lubrication | N/A | N/A | Healing may be hastened by frequent instillation of preservative-free topical lubricants. |
| Rauz, Cell Tissue Bank 2010 (85) | N/A | Autologous serum drops | N/A | N/A | Serum contains a large number of biological substances that are present in tears although some substances are present in lower or higher concentrations. These epitheliotrophic factors are likely to be responsible for the therapeutic effect of serum drops observed in patients with OS disorders over and above conventional commercially available lubricants. |
| Schornack, Clin Exp Optom 2011 (86) | USA, retrospective case review, 18 months | Therapeutic scleral lens<br>n=1 | Clinical assessment | 18 months | A patient presented with a 1-year history of clinically diagnosed LSCD (not due to physical or chemical burns), which was worsening despite aggressive topical and systemic medical therapy. The condition resolved rapidly with initiation of scleral lens wear. The integrity of the OS was maintained for 18 months even after the cessation of lens wear |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| **Conservative surgical options (best supportive care)** | | | | | |
| Anderson, Br J Ophthalmol 2001 (87) | USA, case series of partial LSCD due to chemical burns (n=8), idiopathic (n=3), multiple surgery (n=2), contact lens-related keratopathy (n=2), radiation induced (n=1) and conjunctival intraepithelial neoplasia (n=1), 25.8 months | AMT (n=15, 17 eyes) | Histological assessments, VA, pain, photophobia, safety | Mean 25.8 months (SD 2.5 months) | All eyes exhibited a stable, intact corneal epithelial surface with no eyes developing recurrent erosion or persistent epithelial defect. Mean time to re-epithelialisation 22.8 days. Overall improvement in VA in 92.9% of 14 eyes with visual potential. Of those, five eyes gained ≥6 lines, two eyes gained 4-5 lines, six eyes gained 1-3 lines, and one eye lost 3 lines of Snellen acuity. Pain and photophobia abolished in 86% of cases and substantially reduced in 14%, with all eyes exhibiting decreased vascularisation and inflammation at final follow-up.<br><br>No episodes of postoperative graft infection or rejection. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Dua, Br J Ophthalmol 1998 (88) | UK, prospective study of patients with partial LSCD (n=10) due to: chemical injury (n=6), post-keratoplasty (n=3), SJS (n=1), up to 13 months | Conjunctival epithelium scraping | Clinical examination with slit lamp biomicroscopy, fluorescein staining, photography and planimetry | 3-13 months (mean 7.5 months) | For patients with conjunctival epithelium covering the cornea (n=10), the area of conjunctivalisation had reduced by only 1.2% to 5.6% at the time of the last follow-up visit (group 1).<br>For patients where the advancing sheet of conjunctival epithelium was scraped back to prevent it from crossing the limbus (n=4), complete healing at 10-14 days was observed (group 2, all of whom had chemical burns). |
| Kheirkhah, Arch Ophthalmol 2008 (89) | USA, retrospective case review of patients with moderate to severe LSCD due to recent chemical burns, 16.8 months | AMT (ProKera) (n=5) | Epithelisation, NV | Mean 16.8 months (SD 10.8) | Conjunctival defects reepithelialised in 8.2 days (range, 5-17 days), while limbal and corneal defects healed in 13.6 days (range, 5-25 days). The latter was completed with circumferential closure of limbal defects followed by centripetal healing of corneal defects. In 3 eyes, early peripheral corneal NV was followed by marked regression on completion of healing. During follow-up, all eyes retained a stable surface with improved corneal clarity, and without limbal deficiency or symblepharon. |
| Rauz, Cell Tissue Bank 2010 (85) | UK | AMT | N/A | N/A | Amniotic membrane believed to maintain epithelial progenitor cells within the limbal stem cell niche and facilitate OS epithelial renewal. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| **Conjunctival limbal autograft (CLAU)** | | | | | |
| Dua, Br J Ophthalmol 2000 (90) | UK, case series of patients with unilateral LCSD due to chemical burn (n=3), conjunctival intraepithelial neoplasia (CIN) (n=1), recurrent pterygium (n=1) and contact lens induced keratopathy (n=1), 18.8 months | CLAU (n=6) | Surgical outcomes, VA | Mean 18.8 months (14-31 months) | No intraoperative complications occurred. Postoperatively, the limbal grafts started epithelial outgrowths within the first 2 days and the whole corneal surface was completely epithelialised within 2 weeks, in all cases. No infection, limbal graft failure or slippage of tissue.<br><br>The epithelium was stable, without recurrence of epithelial defects, transparent and smooth. There was no corneal NV.<br><br>Improvement of vision (VA 0.67 in 2 cases and 0.17 in 3 cases, hand movements in 1 case) and symptoms after surgery was substantial in all cases.<br><br>In the donor eyes there were no intraoperative complications, refractive changes, chronic inflammation, persistent epithelial defects or corneal NV. One of the patients developed filamentary keratitis in the donor eye, which was controlled with intense topical lubrication.<br><br>The outcome was satisfactory in all cases: a stable corneal surface was restored and there was a substantial improvement in vision and symptoms. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Kenyon, Ophthalmology 1989 (91) | USA, case series of patients with unilateral (n=17), bilaterally asymmetric (n=7) or bilaterally focal (n=2) severe LSCD due to chemical burns (n=20) thermal burns (n=2), contact lens-induced keratopathy (n=3) and OS failure after multiple surgeries (n=1), 18 months | CLAU (n=26) | Surgical outcomes | Mean 18 months (2-45 months) | Among the 21 patients with follow-up >6 months, nine (43%) had visual improvement to ≥0.2 (moderate visual impairment), and an additional eight patients gained ≥2 Snellen lines of improved VA. In only four patients was vision after limbal transplant either the same or decreased. Rapid surface healing in 19 cases, stable epithelial adhesion without recurrent erosion or persistent epithelial defect in 20 cases.<br><br>Decreased NV in 9 cases, regression of NV in 6 cases and active NV in <1 quadrant in 3 cases.<br><br>No intraoperative complications occurred and, in particular, no inadvertent corneal perforations. No infection, limbal graft failure or sloughing of the grafts occurred.<br><br>The prompt reduction and permanent resolution of chronic external ocular inflammation with decreased irritation and photophobic symptoms and improved cosmesis was uniform.<br><br>Of the six patients who underwent PKP either before (case 25), during (case 7) or after (cases 9, 18, 19, and 23) limbal transplantation, all six eyes attained excellent VA of 1.0-0.3, and all transplanted corneas remained clear and stable without NV. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Moldovan, J Francais d'Ophtalmologie 1999 (92) | France, case series of unilateral LSCD due to chemical burns | CLAU (n=5) | Subjective improvement, VA, histological improvement | 10-47 months | Subjective improvement was recorded in all patients (100%), visual acuity only improved in 1 out of 5 eyes. Histological improvement in the ocular epithelium was recorded in 4/5 eyes. |
| Rao, Cornea 1999 (55) | India, retrospective case study analysis of patients with unilateral severe (Grade III) LSCD due to OS chemical (n=14) or physical (n=2) burns, 3 years | CLAU (n=16) | Surgical outcomes (mean epithelial healing time), VA, symptoms (ocular comfort) | Mean 19.3 ± 13.5 months (3-45) | Limbal autograft transplantation was successful in reconstructing the corneal surface and restoring ocular comfort in 15 (93.8%) eyes. Limbal autografting failed to reconstruct the OS in one patient undergoing surgery 2 weeks after grade IV alkali bums. In 13 eyes with counting fingers or worse vision, functional success (VA>0.05) was attained after surgery in nine (69.2%) eyes. VA ≥0.25 was achieved in two (25%) of eight eyes undergoing surgery for a PED and five of six (83.3%) eyes undergoing surgery after the epithelial defect had healed (p=0.03). Nine patients underwent simultaneous superior and inferior limbal autografting. Mean epithelial healing time in six of these patients undergoing surgery in the acute phase of injury (<4 months) was 15 ± 6.1 days. In three patients undergoing a similar procedure in the chronic phase of injury the healing time was 8.3 ± 6.7 days.<br>7 patients underwent PKP. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| **Limbal epithelial stem cells allografts (CLAL, KLAL)** | | | | | |
| Eslani, AAO 2015 (93) | Retrospective review of patients with LSCD due to chemical burns (n=3) or aniridia (n=2) | KLAL (n=5) | Mean time to acute graft rejection | N/A | The mean time to acute graft rejection was 52.2 ± 7.4 months. The presenting signs in all cases included graft infection and epithelial rejection line. Despite aggressive treatment, all patients developed sectoral LSCD. |
| Han, Graefe's Arch Clin Exp Ophthalmol 2011 (60) | South Korea, retrospective case series of patients with partial or total unilateral (n=20) or bilateral (n=2) LSCD due to SJS (n=5, 6 eyes), chemical or physical burns (n=7, 8 eyes) and other causes (n=9), 47.9 months | KLAL (n=22, 24 eyes) | Absence of persistent corneal epithelial defect, corneal conjunctivalisation or NV on the corneal edge of the graft | 47.9 months | KLAL successful in 33.3% of the eyes. VA ≥0.2 was achieved in 6/22 (27%) of patients. Fifteen episodes of KLAL rejection developed in ten eyes (41.7%), but 13 cases (86.7%) were reversible. Of 45 KLAL procedures, eyelid deformity, symblepharon and the interval of full epithelialisation were significantly associated with KLAL success by univariate analysis, and the presence of symblepharon was identified by multivariate Cox regression analysis as the most important prognostic factor to affect KLAL outcome (p=0.010).<br><br>Raised IOP was reported in 33% of patients, epithelial defect in 42% of patients and symblepharon in 18% of patients.<br><br>There were 3 cases of primary failures (12.5%) and the mean survival time was 20.0±28.4 months (17 days to 114 months). |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Holland, Trans Am Ophthalmol Soc 1996 (94) | USA, retrospective review of patients treated for severe bilateral LSCD due to chemical burns (n=8, 9 eyes), congenital aniridia (n=5, 7 eyes) SJS (n=3, 4 eyes) corneal and conjunctival intraepithelial neoplasia (n=1, 1 eye), epidermolysis bullosa with recurrent ankyloblepharon (n=1) and previous surgery (n=3, 3 eyes), 26.4 months | KLAL (n=21, 25 eyes) | Ocular surface stability, improvement of VA, success of subsequent keratoplasties and preoperative risk factors | Mean 26.4 months (6-63 months) | 72% (18/25) eyes developed a stable OS. 60% (15/25) demonstrated a significant improvement in VA (≥2 Snellen lines; best 0.2). Persistent epithelial defects and symblephara were successfully managed with this procedure. There was 54% rejection rate. 46% (6/13) subsequent keratoplasties were successful. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Huang, Arch Ophthalmology 2011 (58) | China, retrospective non-comparative case series of patients with partial unilateral (n=5) or bilateral (n=12) LSCD due to chemical burns, 16 months | Lr- CLAL (n=17, 17 eyes) | Corneal reepithelialisation, reduction in vascularity, improved corneal clarity and BCVA | 16.0 months (12-26 months) | All eyes achieved epithelialisation mean 10.1 (SD, 1.9) days after surgery. Corneal reepithelialisation, reduction in vascularity and improved corneal opacity seen in all eyes. No eyes demonstrated recurrent epithelial defects or fibrovascular tissue, but gradual recurrence of peripheral corneal vascularisation was observed in 7 eyes. Allograft rejection developed in 3 eyes (17.6%), all of which were successfully treated. BCVA improved in all eyes, and 10 eyes (58.8%) had achieved BCVA ≥0.5, with 15/17 having a VA ≥0.2 (88%) at last follow-up. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Ilari, Ophthalmology 2002 (95) | UK, retrospective, non-comparative case series of patients with severe LSCD due to SJS (n=7), chemical or physical burns (n=8) and others (n=8), 60 months | KLAL (n=20, 33 eyes) | Reconstruction of the OS with restoration of phenotypic corneal epithelium, reduction of corneal vascularisation and conjunctivalisation, decreased pain, and visual improvement | 60 months (15-96 months) | Eight eyes (24.2%) never reepithelialised and were considered primary failures. The remaining 25 grafts initially restored a phenotypic corneal epithelium, but at last follow-up only 7 (21.2%) were stable. Graft survival rate was 54.4% at 1 year, 33.3% at 2 years, and 27.3% at 3 years. VA improved or was unchanged in 19 eyes (82.6%) and decreased in 4 eyes (17.4%). Seventeen corneal transplantations (3 DALK and 14 PKP) were performed either in combination with or after KLAL. All three DALK were successful, whereas 13 of the 14 PKPs failed. Cyclosporine was used initially in high-risk recipients and later in all recipients. Allograft rejection episodes occurred in 13 KLAL procedures of 11 eyes (39.4%) and were more common in patients treated with cyclosporine compared with the untreated group (87.5% vs. 22.2%). Graft survival was longer in the cyclosporine-treated group vs the untreated group.<br><br>Raised IOP was reported in 26% of patients, and corneal necrosis and microbial keratitis each in 13% of patients.<br><br>The final outcome was 30.4% success (69.6% failure). KLAL combined with PKP appeared to have a shorter survival time than KLAL followed by PKP. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Maruyama-Hosoi, Cornea 2006 (96)<br>**NB Cross-referenced from Laing, Arch Ophthalmol 2009** | Japan, retrospective case series of patients with total LSCD due to SJS/ocular cicatricial pemphigoid (n=37, 43 eyes), burns (n=17, 17 eyes), others (n=77, 85 eyes), 46.6 months | KLAL (n=78, 85 eyes) | Graft rejection (epithelial defects, acute oedema, and vascular engorgement as probable signs of immunological rejection) | 46.6 months (mean) | 56/78 (72%) PKP were performed.<br>Graft rejection occurred in 13% of cases.<br>47/85 eyes (55.3%; 41% in patients with ocular burns) had clear grafts at last examination. Eyes with SJS/OCP or burns had a worse prognosis than those with other pathologies (p=0.017).<br>For postoperative complications, 40 eyes (33.1%) showed increased IOP, 10 eyes (8.3%) developed infectious corneal ulcer, 5 eyes (4.1%) had corneal perforation secondary to corneal ulcer and 3 eyes (2.5%) developed retinal detachment. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Tsai, Cornea 1994 (97) | Taiwan, case reports of patients with moderate to severe bilateral LSCD due to physical or chemical burns (n=5), Terrien's degeneration (n=2), congenital sclerocornea (n=1), SJS (n=1) and chronic keratoconjunctivitis (n=7), 18.5 months | CLAL-CD (n=16 eyes) | VA, graft failure, vascularisation | 18.5 ± 5.4 months | Improved VA in 13 eyes (81%: VA 0.67 [n=4], VA 0.8 [n=2], VA 0.4 [n=2], VA 0.2 [n=3] VA 0.1 [n=4]) and rapid (within 1 week) surface healing in 10 eyes (62.5%). Donor limbal tissue developed engorged and tortuous blood vessels in 12 eyes within 1-2 months, but these regressed within 3 months after surgery. No acute graft failure or allograft rejection identified. Twelve eyes (75%) showed total regression of vascularisation and four eyes had decreased vascularisation. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Tsubota, Ophthalmology 1995 (98)<br>**NB Cross-referenced from Laing, Arch Ophthalmol 2009** | Japan, case series of patients with severe bilateral LSCD due to chemical burns (n=3) idiopathic (n=3) moderate ocular pemphigoid (n=2) and traumatic limbal deficiency (n=1) | CLAL-CD (N=9) | OS, VA | 12.3 months (2-17 months) | 5/9 patients achieved OS.<br>VA improved in all nine patients (0.4 [n=3], 0.3 [n=1], 0.2 [n=2], 0.1 [n=2], 0.02 [n=1]). Even though the limbal transplantation provided a stable OS, the final vision did not return to normal in many patients.<br>Aphakia was reported in 56% of patients, bullous keratopathy in 67% of patients, and glaucoma and cataract each in 30% of patients. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| **More than one procedure used (CLAU, CLAL or KLAL)** | | | | | |
| Borderie, J Francais d'Ophthalmologie 2003 (99) | France, case series of patients with LSCD due to severe ocular burns (10 eyes, n=10; chemical in 8 eyes and thermal in 2 eyes), up to 77 months | CLAU in unilateral cases (n=6)<br>KLAL in bilateral cases (n=5) | Ocular stability, VA and PKP success | Mean 36 months (7-77 months) | Success, as assessed by ocular stability, was achieved in 73% of eyes. PKP was performed in 8 patients, with a success rate of 63%. VA improved from 0.4/10 (0.04) to 1.6/10 (0.16). |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Burcu, Cutaneous Ocular Toxicol 2014 (35) | Turkey, retrospective analysis of 40 patients (48 eyes) treated with a range of modalities for LSCD (bilateral, n=8; unilateral, n=20) secondary to moderate to severe chemical burns, 77.2 months | CLAU (n=16)<br>CLAU + lr-CLAL (n=4)<br>Lr-CLAL (n=3)<br>CLAU + KLAL (n=1)<br>KLAL (n=2) | OS stability and CDVA | The mean follow-up was 77.2±35.1 months | Limbal deficiency persisted in 2 of 16 CLAU eyes, which had grade 4 injury.<br>OS stability was not achieved in 1 of 4 eyes that underwent CLAU + lr-CLAL, which had a grade 5 injury. Three patients with bilateral injury achieved acceptable CDVA and OS stability following CLAL.<br>Ocular surface stability was not achieved in a patient with bilateral injury (grade 5 and grade 6) following the KLAL. At the last visit, 30 eyes (62.5%) had an intact and stable OS.<br>Clear cornea was achieved in 11 (78.6%) of 14 eyes with grade 2 injury, in 9 (60%) of 15 eyes with grade 3 injury, in 5 (50%) of 10 eyes with grade 4 injury, in 1 (16.6%) of 6 eyes with grade 5 injury and in 1 (33.3%) of 3 eyes with grade 6 injury clear cornea was achieved. The mean initial CDVA was 1.66±0.99 logMAR. Nine eyes (18.8%) had ≤0.7 logMAR initial VA. The mean CDVA was 0.87±0.85 logMAR at the last visit. There was statistical difference between the initial and last CDVAs ($p<0.001$). At the end of the study, ≤0.7 (≤0.2) logMAR CDVA was obtained in 27 eyes (56.3%). |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Gomes, Ophthalmology 2003 (47) | Brazil, prospective, non-comparative interventional case series in patients with partial or total unilateral (n=6) or bilateral (n=14) LSCD due to chemical burns. Partial LSCD (n=4) and total LSCD (n=16). Latter group had CLAU or CLAL, 10 months | AMT (n=4) in bilateral disease, AMT + CLAU (n=6) in unilateral disease or AMT + lr-CLAL (n=10) in bilateral disease | Reconstruction of corneal epithelium (clear appearance without epithelial defect, normal fluorescein permeability and the absence of conjunctiva-derived goblet cells on impression cytology), decrease in corneal vascularisation and improvement in VA | Mean 19 months (8-27 months) | Satisfactory OS reconstruction was obtained in 15 eyes (75%), with reduced inflammation and vascularisation of the OS and a mean epithelialisation time of 3.3 weeks. Success was observed in all cases of partial LSCD and in 68.75% (11 eyes) of cases of total LSCD (83% success for CLAU +AMT and 60% success for lr-CLAL + AMT). Surgical failure was observed in five severe cases (31.25%). A significant visual improvement was observed in all cases after surgery, except for 2 eyes that maintained preoperative VA. VA ≥0.2 was achieved in 1/6 (17%) in the lr-CLAU + AMT group and 4/10 (40%) in the lr-CLAL + AMT group. PKP was performed in 1/6 (17%) of CLAU + AMT and 5/10 (50%) of lr-CLAL + AMT. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Ivekovic, Ophthalmologica 2005 (100) | Croatia, case series in 15 eyes in patients with unilateral severe (Grade III or IV) LSCD due to chemical burns. 10 of these patients had severe (>6-hour limbal ischaemia), >1 year | CLAU (n=6 eyes) and CLAU + AMT (n=4 eyes) in moderate to severe LSCD patients | Epithelisation, VA, graft rejection | >1 year (7-41 months) | Epithelialisation was complete in 14.5 and 15.3 days, respectively for CLAU and CLAU + AMT. In the 6 patients treated with CLAU, VA ≥0.2 was achieved in 4 patients (67%). In the 4 patients treated with CLAU + AMT, VA ≥0.2 was achieved in 1 patient (25%). No infection, limbal graft failure or slippage of tissue occurred. There were no intraoperative complications, refractive changes or corneal NV in any of the donor eyes. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Meallet, Ophthalmology 2003 (101) | USA, retrospective, non-comparative, interventional small case series of patients with total unilateral LSCD due to chemical burns (n=3), pseudoemphigoid (n=1) and extensive removal of conjunctival intraepithelial neoplasia (n=1), 22 months | CLAU + AMT (n=5) | Symptomatic relief, improvement in VA, fornix deepening, and rapid healing and restoration of normal cornea and limbus in the recipient and donor eyes | 22 months (range, 11-48 months) | All eyes experienced symptomatic relief. All recipient eyes had a mean improvement in VA of nine lines (range, 7-12). The three eyes with stromal vascularisation showed regression, and all recipient eyes had marked improvement in corneal clarity.<br>Three eyes receiving simultaneous symblepharon lysis and fornix reconstruction successfully regained deep, stable fornices. The donor eyes showed rapid healing and restoration of the normal limbal landmark, even in one eye where nearly the entire limbus was removed. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Miri, Ophthalmology 2010 (46) | UK, retrospective consecutive cohort study in 26 (27 eyes) patients with unilateral or bilateral LSCD due to chemical burns (n=13), aniridia-related keratopathy (n=4), 1 patient each with trachoma, contact lens wear, steam injury, ophthalmia neonatum, radiation, chronic keratitis (2 eyes of 1 patient), chronic inflammation, OS intraepithelial neoplasia and unknown, up to 119 months | CLAU (n=12) for unilateral disease, lr-CLAL (n=9) and CLAL-CD (n=6) for bilateral disease | Duration for which a healthy corneal epithelium maintained, VA and QOL (NEI-VFQ) | CLAU: mean 47 months (12-119 months)<br>Lr-CLAL: mean 32.6±28.5 months (13-96 months), CLAL-CD: mean 28.1±36.9 months (22-96 months) | CLAU: Complete re-epithelialisation of cornea within 2 months, of whom 8 patients (67%) had healed within 4 weeks. All patients showed a healthy corneal epithelium until last follow-up.<br>Statistically, CLAU showed significantly better outcome compared with lr-CLAL, which fared better than CLAL-CD (log-rank test $p<0.005$, Wilcoxon [Breslow] test $p<0.01$).<br>CLAL: There were 5 graft failures. Success rate was 89% for lr-CLAL and 33% for CLAL-CD. Improvement in BCVA was seen in 21 eyes (78%; not split out by type of graft). In 1 eye (lr-CLAL) the preoperative VA was maintained but showed subjective improvement by NEI-VFQ.<br>For the cohort, OS failure was seen in 5 cases (19%). Of these, the BCVA deteriorated in 2 eyes (KLAL) and was maintained in 2 eyes (1 CLAL-CD and 1 lr-CLAL); however, in 1 of these (CLAL-CD) the vision had deteriorated subjectively by NEI-VFQ. In 1 eye (CLAL-CD) in which the limbal graft failed after 43 months, the BCVA improved for the first 36 months and then deteriorated to the preoperative level corresponding with OS failure.<br>The overall mean of the VA improved from 0.1 preoperatively to 0.3 postoperatively (all patients). |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Solomon, Ophthalmology 2002 (102) | USA, retrospective, non-comparative interventional case series of patients with total LSCD due to chemical burns (16 eyes), SJS (9 eyes) and other causes, including ocular cicatricial pemphigoid, atopic keratoconjunctivitis, and aniridia (14 eyes), 34 months | KLAL + AMT (n=31, 39 eyes) | Cumulative rates of survival of ambulatory vision (20/200), survival of KLAL, survival of PKP and incidence of complications | Mean 34.0 months (12-117.6 months) | The mean period of ambulatory vision was 23.9 ± 20.9 months (range, 0–104). The overall survival of ambulatory vision was 53.6% at 3 years and 44.6% at 5 years. Twenty-four eyes underwent a total of 45 PKP procedures. KLAL performed alone resulted in higher survival of ambulatory vision at 2 years (86.1% ± 9.1%) vs KLAL + PKP (46.9% ± 10.6%, p=0.100). After 3 years, no difference in ambulatory vision survival was noted between eyes that had simultaneous KLAL + PKP (43.1% ± 30.8%) and eyes that had KLAL alone (39.1% ± 11.4%).<br><br>After 2 years, survival of the second KLAL was better than the first: 68.2% ± 15.4% vs 27.3% ± 13.4%, respectively (p=0.041).<br><br>Ten of 39 eyes (25.6%) developed elevated IOP after surgery. Fourteen eyes (35.9%) developed persistent epithelial defects. Three eyes developed microbial keratitis. One eye with successful corneal surface reconstruction developed postoperative cystoid macular oedema. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Tan, Ophthalmology 1996 (103)<br><br>**NB Cross-referenced from Liang, Arch Ophthalmol 2009** | UK, case series of patients with bilateral LSCD (n=9) or unilateral LSCD (n=9) due to aniridia keratopathy, chronic contact lens-associated epitheliopathy, chemical injury, Stevens-Johnson syndrome, and corneal intraepithelial dysplasia, 27.1 months | Lr-CLAL/CLAL-CD (n=9, 1 with ocular burns) for bilateral disease or CLAU (n=9, 3 with ocular burns for unilateral disease | VA, epithelial healing, symptom reduction, graft rejection | 14.7 months for CLAL (4-24 months)<br><br>27.1 months for CLAU (10 weeks - 46 months) | CLAL resulted in restoration of a stable OS in 7/9 cases, with early visual rehabilitation (VA: 0.67 [n=3], 20/50 [n=2], 0.25 [n=1], 0.1 [n=2], counting fingers [n=1]) and significant reduction in symptoms. Epithelial healing complete within 4 weeks. There were two allograft rejections.<br><br>CLAU resulted in visual rehabilitation in 7/9 eyes (VA: 1.0 [n=1], 0.8 [n=1], 0.67 [n=3], 0.5 [n=2]. There was a significant reduction in symptoms and complete epithelial healing within 3 weeks in all eyes resulting in a stable OS. CLAU failure occurred in two patients (who had chronic contact lens-associated epitheliopathy).<br><br>One contact lens wearer had epithelial dysplasia in the fellow eye at the previous donor site. Subclinical involvement of the fellow eye is suggested as a reason for graft failure and donor eye complications in these eyes. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Titiyal, Ocular Immunol Inflamm 2015 (42) | India, open label, randomised study of patients with severe unilateral LSCD due to chemical or physical burns, up to 22 months | Lr-CLAL (n=10) or KLAL (n=10) | UCVA, BCVA, conjunctivalisation, corneal NV, epithelial defects, corneal clarity, Schirmer's test, TBUT and ultrasonic pachymetry | Lr-CLAL group: 6-22 months.<br>KLAL group: 6-12 months | At 6 months follow-up, the lr-CLAL group had a higher gain in vision (p=0.029), decrease in conjunctivalisation (p=0.009) and increase in Schirmer's values (p=0.009) versus KLAL.<br>Significant improvement in VA was seen in 8/10 patients of the lr-CLAL group and in 5/ 10 eyes of the KLAL group.<br>Regression of corneal NV was seen in 8/ 10 eyes in the lr-CLAL group and 5/10 eyes in the KLAL group.<br>All eyes in both groups had stable OS with no persistent epithelial defects.<br>In the lr-CLAL and KLAL groups, graft failure occurred in 3/10 eyes and 8/10 eyes, respectively.<br>There were no intraoperative complications, such as damage to muscle during symblepharon release or corneal perforation. Up to the minimum follow-up period of 6 months none of the eyes in either group developed any infection or necrosis of cornea. |

| Author, Journal, Year (Study name) | Study location, design, and duration | Interventions | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Torres, Arch Soc Esp Oftalmol 2008 (104) | Spain, case series in patients with unilateral LSCD (40 pterygia, 12 alkali burns, 3 iatrogenic cases, 2 viral infections, 1 neoplasia case) and bilateral LSCD (7 immune-based disorders, 6 alkali burns, 1 iatrogenic case). Up to 115 months | CLAU (n=58)<br>CLAL-CD (n=14) | Stable ocular surface | 20.8 months (3-115 months) | A stable ocular surface was achieved in 81% of CLAU and 7.1% of CLAL patients. |

### 4.11.2 Appraisal of the relevant non-randomised and non-controlled evidence

The results of the above studies must be interpreted with caution because of heterogeneity or lack of study designs; heterogeneity in patient populations in terms of causes of LSCD, degree of disease severity and length of time patients had LSCD; differences in culture methods and carriers substrates; variation in follow-up; and the fact that many patients underwent subsequent/repeated or combined surgical procedures.

*Patient population*

The baseline status for each patient with moderate to severe LSCD differs, both within and between studies. Several patients had previous procedures before limbal stem cell transplantation surgery, including treatment with conventional local therapy including irrigation of the ocular surface, removal of remaining particulate matter, topical antibiotics, lubricants, steroids, superficial keratectomy, conjunctival resection, symblepharon lysis and cycloplegics.(46,91,100–102) In addition, although the focus of this review is LSCD due to ocular burns, the patient population was heterogeneous in many of the studies identified for CLAU(46,90,91,101,103,104) or CLAL/KLAL,(46,60,93–98,102–104) with <30% overall having LSCD due to ocular burns in those treated with CLAU, CLAL or KLAL.

The evidence base to support the use of CLAU is largely comprised of cases of unilateral moderate to severe LSCD, with the exception of one case series of 26 patients, 35% of whom had bilateral moderate to severe LSCD.(91) However, it should be noted that this case series from the US is one that was reported on in 1989 by notable pioneers of the CLAU procedure. Use of CLAU in patients with partial bilateral LSCD was at the time considered experimental and as an extension to previous work. Indeed, CLAU is not used as a treatment option for patients with bilateral LSCD anywhere else in the literature and expert opinion in the UK clearly indicates that CLAU is not used within the NHS to treat patients with bilateral LSCD and has not been undertaken in the UK by the experts consulted.(56,57)

The evidence base to support the use of CLAL/KLAL is largely comprised of cases of bilateral moderate to severe LSCD with limited data in unilateral LSCD.(58,60,95) In contrast, the evidence base to support the use of Holoclar is largely comprised of

cases of unilateral moderate to severe LSCD (95% of cases).(7,8,78,80–83) This variation compromises the ability to compare the results of the different treatment modalities within this review and to draw clinically meaningful conclusions.

*Surgical technique*

A variety of techniques have been reported for limbal stem cell transplantation procedures in the management of severe ocular surface disease. Multiple terms have been used, including limbal autograft transplantation, limbal conjunctival autograft, limbal transplantation, limbal allograft transplantation, homotransplantation of limbal stem cells and keratoepithelioplasty.(34) Different investigators have also used multiple terms to describe the same technique, while the same term has been used for more than one technique.(34) As a result, it is not often clear which of the various procedures is being performed. Although the different techniques have similar goals, they vary depending on the source of the donor and carrier tissue used for the transfer of the limbal stem cells. Carrier tissue is needed in limbal transplantation because it is not technically possible to transfer limbal stem cells alone. The source of donor tissue for limbal stem cell transplantation can be the contralateral eye (autograft), cadaveric whole globe (allograft), cadaveric corneoscleral rim (allograft) or a living relative (allograft).(34) CLAU utilises tissue from the fellow eye and conjunctiva is the carrier. Lr-CLAL is a procedure in which a living relative donates conjunctiva and limbal tissue, whereas CLAL-CD utilises a cadaveric donor for limbus and conjunctiva. Finally, KLAL utilises a cadaveric donor and peripheral cornea is used to transfer the limbal stem cells.

The surgical technique also varies between studies and, in some studies between cases.(35,42,46,55,58,60,90,91,96–98,100–103) In addition, the limbal graft surgery was often combined with other procedures, such as lamellar keratoplasty, PK, cataract extraction, amniotic membrane transplantation, or a combination thereof. (46,47,91,95–98,100–102)

Compared to CLAU and lr-CLAL, Holoclar is minimally invasive, requiring only 1-2 $mm^2$ of limbal tissue(6) versus 4-6 $mm^2$ for CLAU, lr-CLAL from both the superior and inferior portion of the limbus of the donor eye (8-12 $mm^2$ in total).(25,35,44,55,58,103)

*Clinical endpoints*

A total of eight studies investigating CLAU, CLAL or KLAL defined clinical endpoints, all of which were based on efficacy and were measured across a broad range of time points (discussed below). These varied from study to study and included the following:

- Anatomic success, defined as the regression of corneal surface vascularisation with improved ocular surface comfort and complete epithelialisation of the cornea(55)
- Functional success defined as VA >20/400 after CLAU(55)
- Corneal reepithelialisation, reduction in vascularity, improved corneal clarity and BCVA(58)
- OS, improvement of VA and success of subsequent keratoplasties(94)
- Successful ocular surface reconstruction defined as central corneal epithelialisation(96)
- Success defined as absence of persistent corneal epithelial defect, corneal conjunctivalisation or NV on the corneal edge of the graft(60)
- Success defined by the absence of a persistence corneal epithelial defect, on-going inflammation or recurrence of a pterygium(104)
- Surgical success measured by the duration for which a healthy corneal epithelium was maintained after LSCT(46)
- Visual success measured by improvement in VA in the operated eye during the follow-up period(46)
- OS and CDVA(35)

Consequently, it is difficult to compare or combine the results of these studies for CLAU and CLAL/KLAL. It is also difficult to ascertain the relatively safety and tolerability of these procedures due to the lack of detailed reporting of AEs in studies for CLAU and CLAL/KLAL.

In contrast, the primary and/or secondary endpoints for studies investigating Holoclar were well defined and included both efficacy and safety endpoints.

The primary endpoints, assessed at 12 months, for the published Holoclar studies were:(8,78,80,81)

- Restoration of the corneal surface and long-term stability, symptoms, VA
- Resolution of symptoms and restoration of a transparent, avascular and stable corneal surface as assessed by investigator
- Clinical parameters of LSCD (stability/transparency of the corneal epithelium, superficial corneal vascularisation and pain/photophobia), VA, cytokeratin expression on impression cytology specimens and histology on excised corneal buttons
- Full success (all symptoms had disappeared and a transparent, avascular and stable corneal surface had been restored), partial success (most symptoms had disappeared but superficial NV had occurred, even if only sectorial) and failure (persistence of symptoms, recurrent epithelial defects, pannus and inflammation), VA and safety

The primary endpoint, assessed at 12 months, for the Holoclar HLSTM01 study was:(7)

- Success based on superficial corneal NV as 'none' or 'mild'; epithelial defects classified as 'none' (no staining) or 'tracing' (minimum staining)

The secondary endpoints, assessed at 12 months, for the Holoclar HLSTM01 study were:(7)

- Change in symptoms (pain, burning, photophobia), inflammation and VA
- Number of ACLSCTs in each patient
- Number of successful keratoplasties after ACLSCT
- Evaluation of impression cytology: percentage of K3+, K3-, K12+, K12-, K19+, and K19- cells, and presence of caliciform cells

The primary endpoint, assessed between 1-5 years (mean 33.9 months), for the Holoclar HLSTM02 study was:(82)

- Number of subjects experiencing AEs and the number of AEs

The secondary endpoints, assessed between 1-5 years (mean 33.9 months), for the Holoclar HLSTM02 study were:(82)

- Rate of ASCLCT recorded as success or failure based on investigator's judgement
- Number of ASLSCTs in each patient
- Number of successful keratoplasties after transplantation

The primary endpoint, assessed from 90 days after transplantation, for the Holoclar HLSTM04 study was:(83)

- Safety and efficacy of ACLSCT in restoring normal and corneal epithelium

The secondary endpoint, assessed from 90 days after transplantation, for the Holoclar HLSTM04 study was:(83)

- Safety of ACLSCT, including biopsy, surgical procedure and post-surgical treatments in terms of AEs, SAEs, ADRs and serious ADRs

The patients in the Holoclar studies will be followed up for 10 years.

*Duration of follow-up*

The follow-up period between studies varied. For both CLAU and CLAL/KLAL, they ranged from a mean of 12 months(98,100) to 9.4 years.(94) There were eight studies that exclusively investigated and reported treatment outcomes after 12 months, and up to 9.4 years in patients with ocular burns, five for CLAU (n=46),(35,47,55,92,100) and three for CLAL/KLAL (n=27).(42,47,58)

For the published Holoclar studies, patients in the Marchini study were assessed at 12 months and follow-up times ranged from 12 to 50 months.(78) In the Pellegrini 2013 study, patients were assessed at 12 months and then up to 14.5 years (mean 8.4 years).(80) In the Rama 2001 study patients were assessed at 12 months and up to 27 months.(81) In the Rama 2010 study, patients were assessed at 12 months and up to 10 years (mean 2.91 years).(8) The patient populations of Rama 2010(8)

and HLSTM01(7) have significant overlap as the former includes long-term follow-up data derived from many patients included in the latter.

For the unpublished Holoclar studies, primary endpoints were assessed at 12 months for the Holoclar HLSTM01,(7) between 1-5 years (mean 33.9 months) for the Holoclar HLSTM02 study(82) and from 90 days after transplantation for the Holoclar HLSTM04 study.(83)

### 4.11.3 Quality assessment of the relevant non-randomised and non-controlled evidence

There are no prospective RCTs investigating the treatment of moderate to severe LSCD due to ocular burns or comparing Holoclar with SOC therapies. The current published evidence is largely based on non-randomised, non-controlled and retrospective case series.

There has been one open label, randomised study of 20 patients with severe unilateral LSCD due to physical or chemical ocular burns that compared CLAL to KLAL.(42) The findings of this study suggest that although both procedures may be successful in achieving OS (100% in both groups) improvements in VA are more likely to be observed with CLAL (80%) than with KLAL (50%).

Two studies for CLAU,(47,90) one study for CLAL(47) and two studies for Holoclar(78,80) use prospective designs.

As all the studies for SOC and Holoclar are observational and largely without a control group(s), they have an inherently weak study design from which to obtain (and compare) evidence on clinical effectiveness and safety. However, they are the only form of research evidence available, although their results must be interpreted with caution due to the nature of the study designs.

Holoclar is currently the only medicinal product indicated for moderate to severe LSCD due to ocular burns to have been formally studied in clinical trials.

*Joanna Briggs Institute (JBI) analysis*

With regard to the studies investigating CLAU, CLAL, KLAL and Holoclar the quality of the data was rated based on the JBI checklist for case series.(105) Using the JBI

checklist, 10 questions were asked for each study. A ‘yes’ answer received a ‘1’ score and a ‘no, ‘unclear’ or ‘not applicable’ answer received a ‘0’ score. A maximum score of 10 could be achieved.

The JBI analysis for SOC found that only 7 out of 22 studies achieved a score of 5 or more. Only one question was positively answered by the majority of the studies (≥12 out of 22 studies): *Were the outcomes or follow-up results of cases clearly reported?* For the remaining questions, approximately one third or less of studies for SOC were able to provide answers.

The JBI analysis for Holoclar found that all 7 studies(7,8,78,80–83) achieved a score of 5 or more. Eight questions were positively answered by the majority of studies (≥4 out of 7 studies), with 5 questions positively answered for all 7 studies.

Full details of the JBI analysis are provided in the systematic review report for Holoclar, see Appendix 4.

*CONSORT statement analysis*

A similar analysis was performed using a checklist of the internal validity items stated in the 2010 CONSORT table.(106) Using the CONSORT internal validity items, the studies were given a score of 1 for a ‘yes’ for each item and 0 for a ‘no’. The total score for each study is given in the last column and the higher the score, the better the quality of the study. The maximum score that could be achieved was 10. Although this tool is limited, as it is designed for randomised controlled trials, it was thought to provide an alternative and useful method of analysing the data. With this tool, non-randomised, non-controlled studies can score a maximum score of 7.

There are no randomised, controlled, blinded studies for CLAU or CLAL/KLAL in the treatment of moderate to severe LSCD due to ocular burns.

The scores for the 11 studies providing data on CLAU ranged from 1-4 and the scores for the 15 studies providing data on CLAL/KLAL ranged from 1-5. A total of 4/11 and 8/15 studies provided pre-defined primary outcomes for CLAU and CLAL/KLAL, respectively. A total of 3/11 and 5/15 provided statistical analysis and 10/11 and 14/15 provided baseline data for CLAU and CLAL/KLAL, respectively.

There are no randomised, controlled, blinded studies for Holoclar in the treatment of moderate to severe LSCD due to ocular burns.

The retrospective, non-randomised, non-controlled Holoclar clinical trials,(7,82,83) each achieved a score of 6, out of a maximum score of 10. Each of the four published studies for Holoclar(8,78,80,81) achieved a score of 3. The mean score across all Holoclar studies was 4.29. All of the Holoclar clinical trials and published studies provided pre-defined primary or primary/secondary outcomes, statistical analyses of outcomes and baseline data.

Full details of the CONSORT analysis are provided in the systematic review report for Holoclar, see Appendix 4.

### 4.11.4 Bias assessment of the relevant non-randomised and non-controlled evidence

The issue of bias is an important one, especially in rare disease where there is typically little published evidence. The studies investigating the treatment of moderate to severe LSCD due to ocular burns are largely observational and non-comparative. They differ in evaluation methods, baseline characteristics and duration of follow-up. Evaluation of potential bias was conducted on an individual study basis by expert review and by quality assessment.

Plots of treatment effect for the entire population of each study according to size of study were generated. The two treatment effects were percentage of patients who achieved OS and percentage of patients with improvement in VA.

**Figure 9: Results of assessment bias for Holoclar**

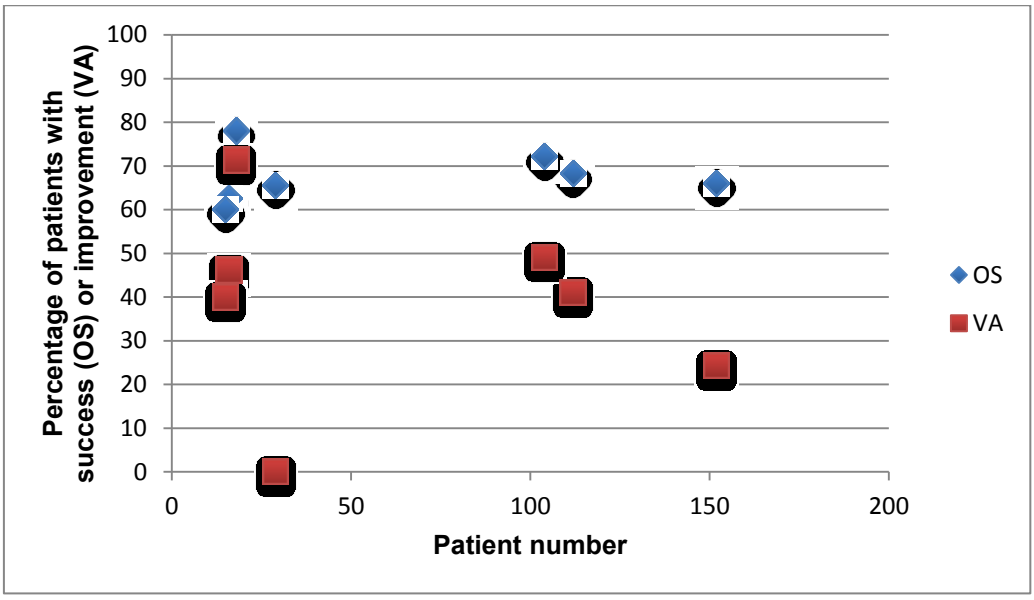



**Figure 10: Results of assessment bias for CLAU**

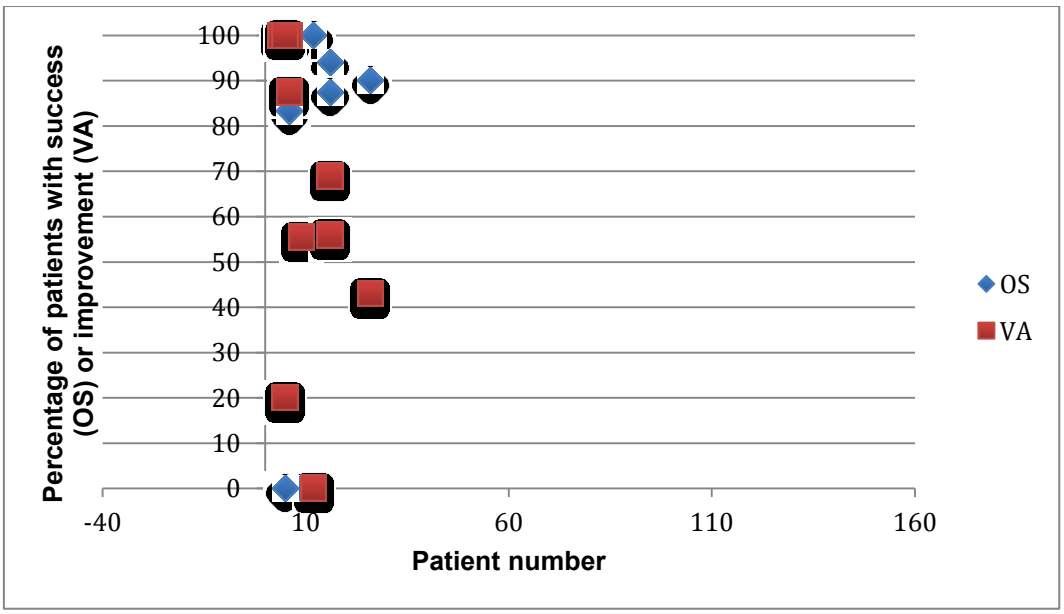
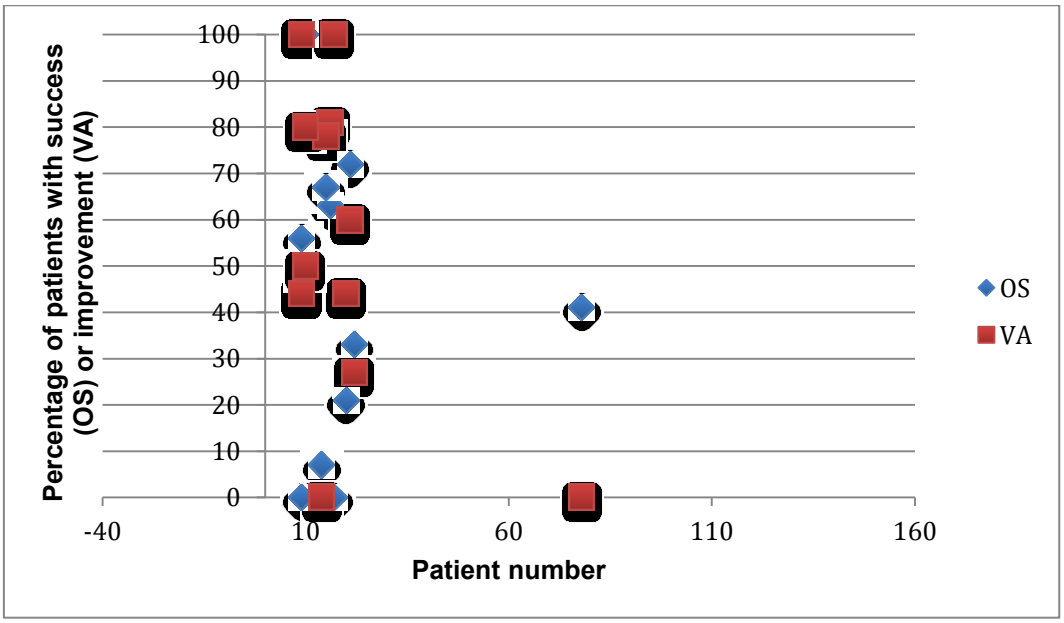


**Figure 11: Results of assessment bias for CLAL/KLAL**




For the percentage of patients achieving OS the outcomes for the Holoclar studies were tightly grouped (between 60-78%). The results for CLAU were also tightly grouped (between 83-100%) but were limited by the size of population being analysed. The results for CLAL/KLAL were very variable (ranging from 7% to 100% success), and also limited by their patient population size.

For the percentage of patients achieving an improvement in VA all the studies was quite variable, with the most variability seen for CLAU and CLAL/KLAL. The three largest studies were for Holoclar. The results for CLAU and CLAL/KLAL were limited by patient population size.

Variability in results for CLAU and CLAL/KLAL could be due to a number of factors. Firstly, the patient population being treated were not homogeneous, with a broad range of aetiologies of LSCD; secondly, the surgical procedures and post-surgical management were not uniform across all studies; thirdly, the definition of clinical success varied across CLAU and CLAL/KLAL studies; and finally, the patient numbers were small. In the CLAU or CLAL/KLAL studies the issue of bias, in terms of lack of representativeness, missing patients, data quality, missing information or open assessment, was not addressed.

In contrast, the criteria for success for Holoclar were pre-defined and are consistent with those used in clinical practice to assess treatment outcomes; the same surgical procedure was followed for all patients, ensuring consistency in delivery; similar post-surgical management was provided for all patients, including antibiotic and anti-inflammatory therapy as per keratoplasty protocols; and there was availability of photographic records of the affected eye for most patients, which provided objective evidence of the effect thus reducing the element of assessment bias, an inherent risk with retrospective data.(107)

In addition, to address the potential for bias in the Holoclar clinical trials, data were re-evaluated in a blinded fashion by an independent assessor. The potential sources of biases in the data collection were investigated and whether this could significantly influence the benefit-risk of the product was assessed. In this context, a prospective protocol (and statistical analysis plan) detailing how to collect and evaluate the retrospective data was generated. The protocol covered all areas of a typical confirmatory study, including the concept, design, conduct and collection of data, as well as data management, analysis and reporting system. Criteria for patient selection and for therapeutic success were based on robust pre-defined endpoints (i.e. before actual data collection) and a statistical analysis plan put in place. In order to address patient selection bias, and ensure consistency of data and applicability to future use, all patients treated with Holoclar were included. The selection criteria in study HLSTM01(7) were modelled on the original study and the 'intention-to-treat' principle was applied to data collection to account for any deviation from the protocol. Study HLSTM02,(82) which sought to collect and analyse safety data, included a more heterogeneous patient population who had received Holoclar, and included patients with LSCD not caused by ocular burns.

Bias relating to the probability of missing data due to the inability to include all patients previously treated was also assessed in the Holoclar clinical trials. In the case of Holoclar, the highly individualised nature of the treatment allowed the sponsor to identify the total number of subjects treated to be 219 between 1998 and 2007 (i.e. up to the time of starting the collection). Of these, only 135 (61.6%) were available for the efficacy and safety analyses in support of the Marketing Authorisation application. Data for the remaining 82 patients were not available as

the investigators declined the invitation to participate and release the clinical data. A more detailed investigation was undertaken to evaluate the risk that this could invalidate the available evidence. Two published studies included 25 of these remaining 82 patients (12 and 13 respectively).(78,81) The results published in these two studies were comparable to the available data of the HLSTM01(7) and HLSTM02(82) studies and supported the positive clinical benefit. It could be concluded that the missing data related to 82 patients did not negate the conclusions on clinical benefit based on the data available on the other 135 patients. In addition, results from sensitivity and subgroup analyses suggested a very low probability that bias would have played a significant role in selection.

Finally, to address bias due to distortions or mistakes in the collection of information, the system for data collection, traceability and analysis for the Holoclar trials followed the ICH-E6 Guideline in Good Clinical Practice.(107) The clinical study protocols and a data management system were defined *a priori* before starting data collection at the clinical sites. A consistent approach to data collection and analysis/review was applied (including training of investigators) and a clinical contract research organisation was appointed for data source verification. A Statistical Analysis Plan was also prepared for each study before database lock. The investigators of the two sites included in the HLSTM01(7) study had both participated in the early clinical testing of the product. During that phase, a data collection form was generated to prospectively gather the key outcome assessment variables, including corneal NV, stability of the epithelium, symptoms, VA etc. This data collection form became part of his or her outpatient health record and was filled in at each patient's visit as standard practice. The study variables were modelled around the available data. In addition, the two investigators collected pictures of the eyes of many treated patients at different occasions. This enabled the re-evaluation of the degree of corneal NV (which was the key element in the definition of the primary efficacy endpoint of the study) by an independent assessor in a blinded fashion. The external evaluation was reported as a secondary endpoint of the study and enabled to verify the absence of a significant degree of reporting bias. Finally, an extensive analysis of missing data (including several sensitivity tests) revealed that the degree of this additional potential issue was minimal and had virtually no impact on the overall results.

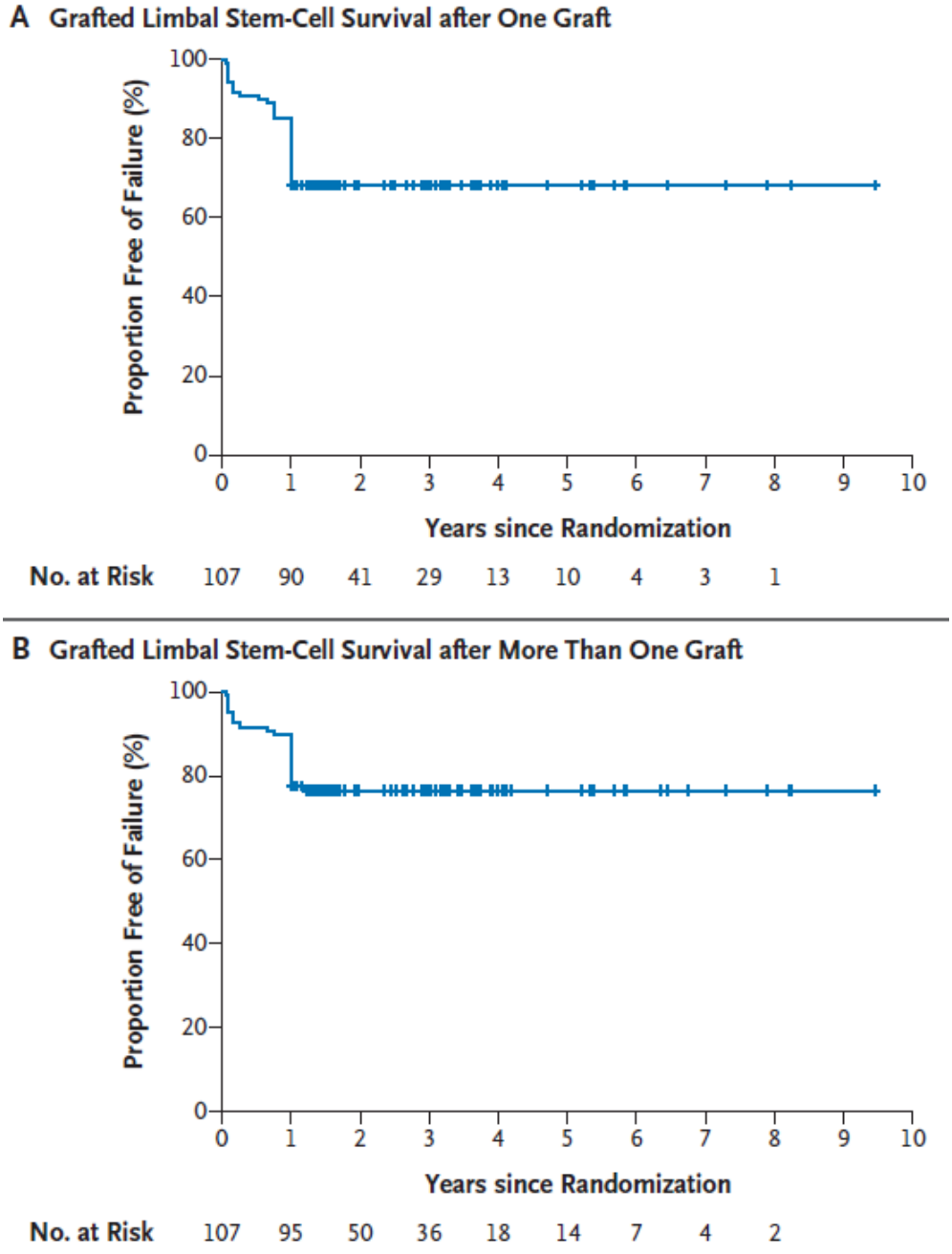
### 4.11.5 Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

*Published data for Holoclar*

The published evidence for ACLSCT with 3T3-J2 feeder cells (Holoclar) for the treatment of moderate to severe or total LSCD due to ocular burns includes five studies, including one proof-of-concept study.(8,78–81) In these studies, the majority of patients had unilateral LSCD. Both short- and long-term data were available (from 4 months to 9 years), which demonstrated restoration of the corneal surface in >75% of patients with associated resolution of symptoms (e.g. burning, pain and photophobia) and long-term stability (>1 year). Keratoplasty (either PKP or DALK) was often carried out after successful grafts to treat residual corneal stromal scarring and improve VA. In three studies there were improvements in VA from hand movements, counting fingers or light perception to a VA ≥0.2 (moderate visual impairment) in >50% of patients.(8,78,81)

One large study by Rama et al,(8) also described the long-term outcome of 113 eyes from 112 patients who received Holoclar between 1998 and 2006. A Kaplan-Meier survival analysis, figure 12, demonstrated that eyes considered successfully treated with Holoclar at 12 months will remain successfully treated up to 10 years of follow-up. In addition, this effect is consistent both for eyes receiving a single Holoclar treatment as well as for eyes that received repeated treatment with Holoclar.

**Figure 12: Kaplan-Meier estimates of grafted limbal stem cell survival**




There is no HRQoL data reported in the clinical studies of Holoclar.

*Unpublished clinical trial data for Holoclar*

There have been three completed clinical trials investigating the efficacy and safety of Holoclar in patients with moderate or severe, unilateral or bilateral LSCD due to ocular burns (HLSTM01, HLSTM02 and HLSTM04).(7,82,83) The details of these

are summarised below. Further information can be found in the EPAR for Holoclar, which is provided as Appendix 2.

HLSTM01 aimed to evaluate the efficacy and safety of Holoclar and HLSTM02 evaluated the safety of the product, with supporting evidence for efficacy. The primary difference between patients evaluated in study HLSTM01 and HLSTM02 was the specific clinical centres involved. In HLSTM01, patients were included from two related, yet distinct clinical sites, which used a standard treatment protocol (pre-treatment assessments, limbal biopsy procedures, cellular expansion, treatment application and subsequent patient follow-up), whereas HLSTM02 encompassed all other available patient data treated at a total of seven other sites. The strategy behind this approach was to generate a sufficiently homogeneous patient population in study HLSTM01 to enable merging of individual patient information into a single composite data set for efficacy assessment, whereas patients in HLSTM02 reflect a more heterogeneous participant population.

*HLSTM01*(7)

The first trial for Holoclar was a retrospective, non-randomised, non-controlled, multicentre observational case series conducted over 12 years (1998 to 2010) in 106 patients (113 transplants; 7 repeats) with moderate to severe unilateral or bilateral LCSD due to ocular burns. In HLSTM01, 90% of patients enrolled had severe loss in VA and 87.5% had deep stromal vascularisation at baseline.

This primary aim of this study was to determine the efficacy of Holoclar.

A total of 104 patients were included in the ITT population, 99 patients were included in the per-protocol population and all 113 transplantation cases were included in the safety population. Patients were observed for 12 months and followed up to 10 years from transplantation.

The primary efficacy endpoint of this trial was rate of success of ACLSC transplantation based on stable corneal epithelium without significant recurrence of NV at 12 months post-intervention. In the ITT population (including missing data imputed as failure), success was reported in 75 patients (72.1%; 95% CI: 62.5-80.5%). In the sensitivity analysis (on-treatment) of the ITT population (without missing data), success was reported in 75 patients (75.8%; 95%CI: 66.1-83.8%). An

independent assessor evaluated treatment outcome in 46 patients with both baseline and Month 12 photographic evidence showing good consistency with the result in the overall ITT population: 31 out of the 46 cases (67.4%) were considered a treatment success.

The main secondary efficacy endpoints included symptom resolution (pain, burning and photophobia), inflammation, NV, VA, number of successful keratoplasties after LSCT and safety. The number of patients with symptoms significantly decreased from the pre-surgical assessment (40 patients; 38.5%) to 1 year after the procedure (12 patients; 11.5%; p<0.001), including pain (7 [6.7%] patients reported pain pre-surgery and all 97 evaluated patients had no pain at 1 year [93.3%]), burning (30 [28.8%] patients reported mild to moderate burning pre-surgery and 7 [6.7%] reported mild burning at 1 year) and photophobia (35 [33.7%] patients reported mild to severe photophobia pre-surgery and 8 [7.7%] reported mild photophobia at 1 year). The level of inflammation remained unchanged at 1 year from pre-surgical levels (30.8% versus 31.7%). However, the intensity of both limbal hyperaemia and bulbar hyperaemia progressively improved over time. Superficial NV significantly decreased from pre-surgical levels to 1 year (63.9% versus 93.8%, p<0.001). Overall, VA was improved by at least 1 line in 49% of patients (95%CI: 39.4-58.6%) and in 83.3% (95%CI: 66.1-100.0%) of those without stromal scarring (n=15/18). Furthermore, clinically relevant improvement of VA of 3 lines was observed in 38.5% (40/104) of the patients and half of the patient with off-chart vision at baseline gained on-chart vision after Holoclar treatment.

Fifty-seven patients underwent at least one post-graft keratoplasty, and 24 of them (42.1%) had at least one successful keratoplasty. In this group 32 patients (57.1% including missing values) had at least one line improvement in VA after the first keratoplasty while 18 patients did not improve (14 were stable and only 4 had a worsening in VA) after the 1-year follow-up visit. Changes of ≥3 lines/categories were observed in 21 cases (corresponding to 65.6% of improvers and 37.5% of the overall group including missing values). In 6 patients, there was not sufficient data to assess change in VA.

A total of 194 AEs were reported in a total of 73 transplantation procedures (64.6%) over a follow-up period of 36.8 ± 23.0 months (range 1.05-118.5). Overall, six SAEs (three fatal) were reported after six transplantation procedures (5.3%), all in subjects

with one transplantation (5.9%). None of them was considered as treatment-related. A total of 22 ADRs were reported after 19 transplantation procedures (16.8%). There were no ADRs potentially related to antibiotics up to 1 month after transplantation. AEs potentially related to corticosteroids (occurring up to 3 months after transplantation) were reported in six cases (5.3%), five consisted of glaucoma and one of gastritis. Only one case of glaucoma was considered by the investigator to be treatment-related (i.e. as ADR).

**Key findings from HLSTM01**

- The primary aim of this study was to determine the efficacy of Holoclar
- Holoclar was associated with a successful outcome (i.e. a stable corneal epithelium without significant recurrence of NV at 12 months post-intervention) in a significant proportion of cases (72.1%; ITT population), significantly exceeding the pre-defined hypothesis of at least 50% of successful cases. An independent assessor showed good consistency with 31 out of 46 cases (67.4%) considered a treatment success
- The proportion of patients presenting any degree of superficial NV significantly decreased from the pre-surgical visit to the follow-up at 12 months (63.9% versus 93.8%, $p<0.001$)
- The proportion of patients with symptoms significantly decreased from the pre-surgical visit to the follow-up at 12 months after transplantation (11.5% versus 38.5%, $p<0.001$), with progressive improvements in the intensity of pain, burning and photophobia
- The intensity of both limbal hyperaemia and bulbar hyperaemia at eye examination progressively improved over time
- Improvement of at least one line in VA was reported in almost half of cases
- Successful keratoplasty after Holoclar was observed in >40% of cases
- Overall, the transplant procedure and the following post-transplantation treatments were well tolerated, with no SAEs considered related to Holoclar

*HLSTM02*(82)

The second trial for Holoclar was a retrospective, non-randomised, non-controlled, multicentre observational case series conducted over 9 years (2001 to 2010) in 29 patients with moderate to severe unilateral or bilateral LCSD due to ocular burns.

The primary aim of this study was to determine safety.

The primary endpoint of this study was to evaluate the safety of the ACLSC transplantation both in terms of the number of subjects that experienced AEs and the number of AEs.

The secondary endpoints were the outcome of the ACLSCT in terms of success or failure based on Investigator's judgement; the number of ACLSCT in each patient; the number of successful keratoplasties after ACLSC transplantation and the relative content of corneal and conjunctival epithelial cells by impression cytology.

A total of 29 patients were included in the safety population and secondary analyses.

A total of 46 AEs were reported in 19 patients (65.5%), of these 21 events occurred in 10 patients (34.5%) were judged as ADRs. A total of 10 AEs reported in six patients (20.7%) were defined of "severe intensity". Eye disorders were the most common group of AEs observed, with eye pain (in 17.2% of patients) and glaucoma (13.8%) as the most common single events reported. Corneal graft (keratoplasty) rejection was reported in two cases (6.9%). Another patient had other graft complications. There was one case of corneal infection after transplantation. Five SAEs were reported in 3 patients (10.3%) and 10 AEs of severe intensity were reported in 6 patients (20.7%). Three SAEs in two patients were considered as being treatment-related: syncope vasovagal in one patient, and ulcerative keratitis and corneal perforation in another. None of the AEs led to study withdrawal.

According to investigator's judgment, success was reported in 19 patients (65.5%; 95%CI: 48.2-82.8%), failure was reported in six patients (20.7%) and the information was missing for four patients (13.8%). During the period of observation included in the study, all patients received one transplantation. Only one patient had one ACLSC graft performed before inclusion in the study. Six patients underwent one or more keratoplasties after ACLSC transplantation. In four of these (66.7%), at least one successful attempt was recorded. Of the six cases with one or more post-ACLSC transplantation keratoplasties, three (50.0%) had a history of failed keratoplasty

before ACLSC transplantation, but reported a successful outcome in at least one of the post-ACLSC keratoplasties. In one patient (16.7%) with successful keratoplasty before ACLSC transplantation, the post-ACLSC transplantation keratoplasty information was missing. Among the two patients naïve to keratoplasty, one of them was considered a failure in the post-ACLSC transplantation keratoplasty, whereas the other had a successful outcome in at least one keratoplasty attempt. After transplantation, the mean percentage of CK3+ cells was higher (32.3% versus 21.7%) and CK19+ cells lower (21.4% versus 37.3%) than what observed at the pre-surgical visit, if all available data were considered in the analysis (i.e. 20 and 23 subjects respectively at pre-surgical visit, and 11 subjects after transplantation). However, if only the small subgroup of patients with valid values both at the pre-surgical visit and after transplantation was considered (n=9 for CK3 and n=10 for CK19), the observed changes were not statistically significant for either variable (p=0.865 and p=0.417, respectively).

**Key findings from HLSTM02**

- This primary aim of this study was to determine the safety of Holoclar
- Overall, the transplant procedure was well tolerated: eye disorders consisting of known post-procedural AEs were the most common AEs
- Corneal graft rejection and other major complications were reported in a minority of cases
- ACLSC transplantation was associated with a successful outcome in the 65.5% of cases

*HLSTM04*(83)

The third trial for Holoclar was a retrospective, multicentre, observational case series conducted over 5 years (2008 to 2013) in 15 patients with moderate to severe unilateral or bilateral LCSD due to ocular burns. This study included all patients who underwent ACLSCT after the period covered by studies HLSTM01 and HLSTM02 in three Italian sites. These centres accounted for 100% of the patients treated with Holoclar since 2008 in Italy and data were collected for all the patients treated.

This primary aim of this study was to determine safety and efficacy.

The primary safety endpoints of this study were to evaluate the:

- AEs, SAEs, ADRs and serious ADRs relating to biopsy, surgical procedure and postsurgical treatments
- Solicited ocular symptoms (i.e. eye pain, burn and photophobia)

The primary efficacy endpoints of this study were to evaluate the:

- Degree of superficial corneal NV before and after ACLSCT
- Degree of corneal epithelium integrity before and after ACLSCT
- Outcome of ACLSCT (based on the combination of superficial corneal NV and corneal epithelium integrity)
- Presence and severity of clinical symptoms (pain, burning, photophobia) before and after ACLSCT
- Presence and severity of inflammation before and after ACLSCT
- Best-refracted VA before and after ACLSCT

A total of 15 patients were included in the safety and efficacy populations.

The safety analysis showed a favourable safety and tolerability profile. Sixty percent of patients presented with TEAEs, the most frequent being eye disorders and nervous systems disorders. Only one SAE (stroke) was reported; this was severe in nature, not related to the procedure. No deaths or ADRs were reported. Inflammation (limbal and bulbar hyperaemia) was observed to occur with a slight increase in frequency at the first follow-up visit (3-4 days post-transplant), which was expected due to the recent operative procedure. The frequency for limbal hyperaemia was higher than bulbar hyperaemia. The occurrence of hyperaemia did not represent a limiting factor for the success of the treatment. Due to the high percentage of missing data at baseline, no definitive interpretation of the clinical symptoms (pain, burning and photophobia) could be made.

Overall, nine out of 15 patients had ACLSCT success (60%) at the Day 90 follow-up, which was maintained up to the last visit (mean 217 days [range: 85-777 days]).

The superficial corneal NV exhibited a good improvement. At the pre-surgical visit 80% patients presented with four quadrants involved and the remaining 20% patients with three quadrants involved. At both post-transplantation visits 67% of patients achieved successful resolution of NV (no superficial corneal NV or only one quadrant

involved) and 33% patients had moderate or severe NV at both post-transplantation visits.

There was a decrease of 75% in central corneal involvement (13% of patients at both post-transplantation visits versus 87% of patient pre-surgically). The corneal epithelium integrity was improved from 40% of patients without defects at the pre-surgical visit to 60% and 73% of patients at the Day 90 and last visits, respectively. The percentages of patients with trace defects reduced from 47% at the pre-surgical visit to 20% and 13% at the Day 90 and last visit, respectively. The number of mild corneal defect decreased from 13% at the pre-surgical visit to 7% at the last visit. Only 7% of patients had a severe corneal epithelia defect at the post-transplantation last-visit.

The presence of clinical symptoms (pain, burning and photophobia) was noted in a few patients at the pre-surgical visit. These symptoms were maintained or exhibited an apparent increase, mainly due to missing data, at the post-transplantation visits. The assessment of all symptoms showed 13% patients had at least one symptom at the pre-surgical visit; by Day 90 this increased to 27% patients, and at last visit was 33% patients. However, it is important to highlight that data analysis with respect to symptoms is not conclusive, neither for safety or efficacy assessment, due to the large amount of missing information at the baseline (60.0%).

Limbal hyperaemia was slightly increased at Day 90 (from 13% patients with mild limbal hyperaemia to 20% patients with mild limbal hyperaemia). One patient (7% of the population) developed moderate limbal hyperaemia in conjunction with blepharitis. Similarly, at the last visit 13% patients had mild or moderate limbal hyperaemia mainly in conjunction with blepharitis. There was a slight transient increase in the frequency of bulbar hyperaemia, from 40% patients with mild bulbar hyperaemia at the pre-surgical visit to 53% patients at Day 90, which decreased to 33% of patients at the last visit.

VA was assessed for both NVA and BCVA and expressed as LogMAR. A decrease in LogMAR equates to an improvement in VA. Ninety-three percent (n=13) of the study population had stromal scarring, so a direct functional benefit from the procedure was not expected. However, there was a significant decreased in NVA from 2.2 at the pre-surgical visit to 1.9 LogMAR at Day 90 (n=13 [one patient without

stromal scarring had missing data for this time point]; p=0.028) and 1.8 (0.6) LogMAR at the last visit (n=14; p=0.026). Based on the data collected from HLSTM01, patients with stromal scarring would be ideal candidates for re-treatment with Holoclar and keratoplasty. For these patients, VA improvement would be expected after keratoplasty, while treatment with Holoclar would provide limbal stem cell replenishment for sustaining long-term keratoplasty success.

According to the Investigator's judgment, treatment failure occurred in two patients, both presenting at the pre-surgical visit with compromised ocular conditions.

**Key findings from HLSTM04**

- The primary aim of this study was to determine the safety and efficacy of Holoclar
- The safety analysis showed a favourable safety and tolerability profile
- Nine out of 15 patients had ACLSCT success (60%)
- The superficial corneal NV exhibited a good improvement, with 67% of patients achieving successful resolution of NV
- There was a decrease of 75% in central corneal involvement (13% of patients at both post-transplantation visits versus 87% of patient pre-surgically)
- Limbal and bulbar hyperaemia increased slightly by the last visit compared to pre-surgical levels (13 mild or moderate [n=2] versus 13 mild for limbal hyperaemia [n=2] and 53% mild or moderate [n=8] versus 47% mild or moderate [n=7] for bulbar, respectively)
- Significant improvements in VA were achieved at both Day 90 (p=0.028) and last visit (p=0.026) despite the majority of study population exhibiting stromal scarring
- Due to the high percentage of missing data at baseline, no definitive interpretation of the clinical symptoms (pain, burning and photophobia) could be made

*Published data for conservative management (best supportive care)*

Currently, LSCD can be managed conservatively, either non-surgically with eye drops, lubricants or contact lenses, or surgically with epithelial corneal scraping or AMT. There are no formal comparative studies and, by nature of the condition and interventions, there is no randomisation or blinding of interventions. There is limited evidence for non-surgical intervention, with only one published case series reporting on the use of scleral lenses in patients who had LSCD not due to physical or chemical burns.(86) There is one prospective case series on conjunctival epithelial scraping in 4 patients with chemical induced LSCD post-keratoplasty.(88) There have been two small case series on AMT use, one in patients with moderate to severe LCSD due to ocular burns (n=5) and one in a heterogeneous patient population with partial LSCD, of whom eight were due to ocular burns.(87,89)

*Published data for CLAU, CLAL and KLAL*

There is a greater body of published evidence for the use of CLAU, CLAL or KLAL than for conservative management, but this is also largely based on case series and very heterogeneous in terms of the patient populations (causes of LSCD and degree of severity of LSCD at baseline). Most studies included patients with a range of causes of LSCD.

In the majority of cases, unilateral LSCD was managed with CLAU(46,55,90–92,99–101,103,104) and in all but one case, bilateral LSCD was managed with CLAL or KLAL.(35,46,47,58,60,94,99,103) There was one record of CLAU being used to manage bilateral LSCD.(91) However, it should be noted that this case series from the US is one that was reported on in 1989 by notable pioneers of the CLAU procedure. Use of CLAU in patients with partial bilateral LSCD was at the time considered experimental and as an extension to previous work. Indeed, CLAU is not used as a treatment option for patients with bilateral LSCD anywhere else in the literature and expert opinion in the UK clearly indicates that CLAU is not used within the NHS to treat patients with bilateral LSCD and has not been undertaken in the UK by the experts consulted.(56,57)

In some case series, unilateral LSCD was managed with CLAL or KLAL(58,94) or the type of LSCD (either unilateral or bilateral) was not defined.(93,95,96) In three

case series from 1994-2010 CLAL from a CD was used,(93,97,98) in four cases series from 2003-2015 lr-CLAL was used,(35,42,47,58) and in two case series both were used.(46,103) The OS and VA outcomes were independent of the source of CLAL.

There was a range of primary clinical outcomes reported, e.g. histology (epithelialisation), VA, OS outcomes, symptom improvement (pain, inflammation etc.), NV and rejection (allograft). There is no single universally accepted standard endpoint for assessing clinical outcomes in LSCD.

In some cases clinical outcomes were reported on an individual patient basis or else grouped rather than stratified by cause of LSCD. Due to the design of the case series and the small patient numbers, there was limited statistical analysis or the statistical analysis was not relevant to the endpoints of interest in this review. Finally, in some case series there was more than one intervention non-comparatively assessed (CLAU, CLAL, KLAL, CLAU + AMT, CLAL + AMT, CLAU/CLAL/KLAL followed by keratoplasty and finally CLAU + CLAL and CLAU + KLAL). The impact of treatment on HRQoL was not assessed in any of the studies identified.

As it is difficult to present histological findings or symptom improvement in a quantitative manner, success or rejection rates and VA have been described below for all studies that presented this information. In addition, the reported percentage of patients who also underwent PKP is also described.

The VA endpoint varied between these studies and was largely reported on an individual basis as pre- and post- transplantation or reported as the overall percentage of patients with improved VA. The majority of the studies used the Snellen method of assessing VA, with the exception of Ivekovic et al,(100) Huang et al(58) and Han et al(60) who used decimal acuity, and Burcu et al(35) who used LogMAR. For the purposes of providing some uniformity in the VA results and in order to compare between studies, the results summarised below have been converted to decimal acuity.

Six case series were identified were the results were provided for patients treated exclusively with CLAU, with a total of 69 patients (56 of whom had ocular burns).(47,55,90,91,100,101) One of these studies investigated the efficacy of

CLAU, CLAU + AMT or AMT alone.(100) Graft success was reported to have been achieved in ≥83% of patients with moderate, severe or total unilateral LSCD.(47,55,90,91,100,101)

In the first case series, VA ≥0.2 was achieved in 1 patient (17%).(47) In the second case series, VA >0.05 was achieved in 69.2% of patients, symptom improvement was observed in those with graft success and PKP was performed in 44% (n=7) of patients.(55) In the third case series, VA ≥0.167 was achieved in 83.3% of patients, symptom improvement was seen in all patients and PKP was performed in 60% (n=3) of patients.(90) In the fourth case series, VA ≥0.2 was considered a success and was achieved in 43% of patients, there was symptom improvement in all patients and PKP was performed in 23% (n=6) of patients.(91) In the fifth case series, 10 of 15 patients were treated with CLAU (n=6) or CLAU + AMT (n=4). All 10 grafts were considered successful. In the CLAU group, VA ≥0.2 was achieved in 67% of patients (n=4/6) and in the CLAU + AMT, VA ≥0.2 was achieved in 25% of patients (n=1/4).(100) Decimal acuity improvement could not be calculated for the last case series.(101)

In patients treated with CLAL or KLAL, ten case series were identified (including one abstract presented at AAO 2014 and two studies that investigated both CLAL/KLAL and CLAU). In seven studies, VA ≥0.2 ranged from 27% to 69%.(42,58,60,94,97,98,103) The rejection rates in nine studies ranged from 0% to 80%.(42,58,60,94–98,103) In four studies, PKP was performed in 42-72% of cases.(60,94–96)

Few studies reported on corneal NV or improvements in the symptoms of LSCD (pain, burning and photophobia). AE reporting was missing in many studies and changes in HRQoL were not reported in any study. In an attempt to attain additional outcome data for these studies, the authors were contacted and a request was made. We received responses from four authors (Tsubota, Tsai, Eslani and Calonge). No further data could be provided, but the publication of the study by Eslani et al is expected later in 2016.

Tables 13 and 14 (below) summarise the key findings for the clinical effectiveness and safety of the relevant non-randomised and non-controlled evidence for Holoclar

and comparator technologies reporting outcomes relevant to the scope of this technology appraisal. The principle clinical outcomes reported were OS and improvement in VA. The latter was reported as overall VA and not necessarily defined by affected eye only or whole person. For both OS and VA, 95% confidence intervals have been calculated by the Wilson method for the studies where this was not provided in the publications.

## Table 13: Outcome measures for Holoclar

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation/ NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| Marchini, Clin Exp Ophthalmol 2012 (78)<br>n=16 | 100% | 100%/0% | 62.6%<br>Complete restoration of a stable and clear epithelium | 46.2% (95% CI: 23.2% to 70.9%) | 81.3% | 87.5%<br>At 12 months | 62.6% | 62.6% | There were no AEs in 9 patients, Keratectomy occurred in 1 patient, inflammation in 5 patients, fungal keratitis in 2 patients, dellen and corneal ulcer in 1 patient, descemetocele in 1 patient, raised IOP in one patient and keratitis and symblepharon in 1 patient |

## Table 13: Outcome measures for Holoclar

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation/ NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| Pellegrini, Regen Med 2013 (80)<br>n=152 | 95% | 100%/0% | 66.05% of eyes (including repeat procedures)<br>All symptoms disappeared and a transparent, avascular and stable corneal surface had been restored | 24.3% in patients with stromal scarring and who underwent concomitant keratoplasty | 66.05% | 66.05% | 66.05% | 66.05% | During the entire follow-up, no AEs referable to the cultures or to any of the culture components were observed |
| Rama, Transplantation 2001 (81)<br>n=18 | 100% | 100%/0% | 78%<br>Improvement of symptoms (clinical signs) and stable regeneration of corneal | 71.4% (95% CI: 45.4% to 88.3%) | 78%<br>Average score for clinical signs improved from 2.7±0.5 to | 78% | 78% | 78%<br>Average score for corneal cytology improved from 2.8±0.4 to | Persistent inflammation and bleeding, observed during the early postoperative course, in 4 |

## Table 13: Outcome measures for Holoclar

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation/ NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | epithelium (corneal transparency and corneal cytology) | | 0.07± 0.2 | | | 0.8±0.5 | patients who subsequently had failure of their graft |
| Rama, N Engl J Med 2010 (8)<br>n=112 | 98.2% | 85.5%/12.5% | 68.2% first graft<br>76.6% first and second graft (n=9) combined<br>Permanent restoration of a transparent, renewing corneal epithelium<br>For patients | 41% | 68.2% | 68.2% | 68.2% | Cultures that contained more than 3% p63-bright cells led to successful corneal epithelial regeneration in 78% of the eyes | Postoperative complications were reported in 59% of patients with a successful graft and 91% with partial success or failure of graft |

## Table 13: Outcome measures for Holoclar

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation/ NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | only with ocular burns (calculated from supplementary table): 67.3% (95% CI: 59.5% to 74.3%) | | | | | | |
| Chiesi Farmaceutici S.p.A., HLSTM01 2012 (7)<br>n=104 | 97.1% | Not reported | 72.1% for total ITT population (95% CI: 62.5% to 80.5%) 74.5% for ocular burn patients<br>91.7% for repeated treatment | 49.0% (95% CI: 39.4 to 58.6%)<br>83.3% (95% CI: 66.1% to 100.0%) in patients without stromal scarring | 70% | No change (69% without inflammation at baseline and 68% without inflammation at 12 months follow-up) | 73% | 84% | Well tolerated. No serious AEs considered related to Holoclar |

## Table 13: Outcome measures for Holoclar

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation/ NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | Stable corneal epithelium without significant recurrence of NV at 12 months post-intervention | 44.4% (95% CI: 33.6% to 55.3%) with stromal scarring | | | | | |
| Chiesi Farmaceutici S.p.A., HLSTM02 2012 (82)<br>n=29 | 79.3% | Not reported | 65.5% (95% CI: 48.2% to 82.8%)<br>Stable corneal epithelium without significant recurrence of NV at 12 months post-intervention | Not reported | Not reported | Not reported | Not reported | Mean percentage of CK3+ cells increased after transplantation vs pre-surgical cytology from 21.7 to 32.3; mean percentage of CK19+ decreased from | 65.5% of patients experienced AEs, the most frequent being eye disorders |

## Table 13: Outcome measures for Holoclar

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation/ NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 37.3 to 21.4 | |
| Chiesi Farmaceutici S.p.A., HLSTM04 2014 (83)<br>n=15 | 100% | Not reported | 60% (95% CI: 35.8% to 80.2%)<br>Stable corneal epithelium without significant recurrence of NV at 12 months post-intervention | 40% with stromal scarring | No change | 87% with none and 13% mild | 67% | 73% corneal epithelial integrity | 60% of patients experienced AEs, the most frequent being eye disorders and nervous systems disorders |

## Table 14: Outcome measures for comparator technologies

| | Percentage of patients with ocular burns | Unilateral/ Bilateral | Percentage of patients who achieved ocular stability | Percentage of patients with improvement in VA | Percentage of patients with improvement in symptoms (pain, burning, photophobia) | Percentage of patients with improvement in inflammation | Percentage of patients with resolution of vascularisation / NV | Percentage of patients with histological improvements | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| **Conservative non-surgical options (Best Supportive Care)** | | | | | | | | | |
| Schornack, Clin Exp Optom 2011 (86)<br>Therapeutic scleral lens<br>N=1 | 0% | Not reported | Integrity of ocular surface maintained | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| **Conservative surgical options (Best Supportive Care)** | | | | | | | | | |
| Du, Br J Ophthalmol 1998 (88)<br>Corneal scraping<br>N=6 | 67% | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| AMT<br>N=20 | 65% | Not reported | 100%<br>Stable intact corneal epithelial surface | 93% | 86% | Not reported | 100% | No epithelial defects | No rejection or infections |
| **CLAU** | | | | | | | | | |
| Burcu, Cutaneous Ocular Toxicol 2014 (35)<br>N=16 CLAU | 100% | 100%/0% | 87.5% (95% CI: 64.0% to 96.5%)<br>An additional 5 patients underwent CLAU + Ir-CLAL (n=4) and CLAU + KLAL (n=1). In these cases the initial CLAU procedure failed and a second transplant was required. With these cases | 56% (95% CI: 33% to 77%) for total population<br>Not given for subgroups | Not reported | Not reported | Not reported | Not reported | Not reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | taken into account, OS is achieved in 66.7% | | | | | | |
| Dua, Br J Ophthalmol 2000 (90)<br>N=6 CLAU | 50% | 100%/0% | 100%<br>Stable corneal epithelial surface, without recurrence of epithelial defects, transparent and smooth | 100% | 100% | Not reported | Not reported | 100% | No intraoperative complications, infection or graft failure occurred. Postoperatively keratitis occurred in 17% of patients. One patient developed filamentary keratitis along the edge of the donor site. |
| Gomes, Ophthalmol 2003 (47)<br>N=6<br>CLAU + AMT | 100% | 100%/0% | 83.3% (95% CI: 43.7% to 97.0%) | 87.5% (95% CI: 64.0% to 96.5%)<br>total population (not broken out by | Not reported | Not reported | Not reported | Not reported | Not reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | subgroups) | | | | | |
| Ivekovic, Ophthalmologica 2005 (100)<br>N=6 CLAU<br>N=4 CLAU+ AMT | 100% | 100%/0% | CLAU: 100% (95% CI: 61% to 100%)<br>Epithelialisation was complete in 14.5 days<br>CLAU + AMT: 100% (95% CI: 51.0% to 100%)<br>Epithelialisation was complete in 15.3 days | CLAU: 100% (95% CI: 61% to 100%)<br>CLAU + AMT: 100% (95% CI: 51.0% to 100%) | Not reported | Not reported | CLAU: 100%<br>CLAU + AMT: Not reported | Not reported | CLAU: No infection, limbal graft failure or slippage of tissue occurred. There were no intraoperative complications, refractive changes or corneal NV in any of the donor eyes<br>CLAU + AMT: No infection, limbal graft failure or slippage of tissue |
| Kenyon, Ophthalmology 1989 (91)<br>N=26 CLAU | 85% | 65%/35% | 95%<br>Stable epithelial adhesion | 43% | Decreased | Decreased | 43% | Not reported | No intraoperative complications, infections or |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | without erosion or persistent epithelial defect | | | | | | graft failure |
| Meallet, Ophthalmol 2003 (101)<br>N=5 CLAU + AMT | 60% | 100%/0% | 100% (95% CI: 56.6% to 100.0%) | 100% (95% CI: 56.6% to 100.0%) | Not reported | 100% | 40% | Not reported | Transient epithelial defect in one eye and migration of pigmented epithelium onto AMT-covered limbus in one eye |
| Miri, Ophthalmology 2010 (46)<br>N=12 CLAU | 50%<br>(Total population) | 100%/0% | 100%<br>Success measured by duration for which a healthy corneal epithelium was maintained after LSCT | 100% | Not reported | Not reported | Not reported | Not reported | Not reported |
| Moldovan, J Francais | 100% | 100%/0% | Not reported | 20% (95% CI: | Not reported | Not reported | Not reported | 80% | Not reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| d'Ophtalmologie 1999 (92)<br>N=5 CLAU | | | | 4% to 63%) | | | | | |
| Rao, Cornea 1999 (55)<br>N=16 CLAU | 100% | 100%/0% | 94% (95% CI: 72% to 99%)<br>Reconstruction of the corneal surface | 69% (95% CI: 42% to 87%) | 93.8% | Not reported | 93.8% | Not reported | Not reported |
| Tan, Ophthalmology 1996 (103)<br>N=9 CLAU | 33% | 100%/0% | 100% | 55.5% | 100% | 77.8% | 0% | 100% | CLAU failure occurred in two patients (who had chronic contact lens-associated epitheliopathy).<br>One contact lens wearer had epithelial dysplasia in the fellow eye at the previous donor site. Subclinical involvement of the fellow eye is suggested as a reason for |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | graft failure and donor eye complications in these eyes |
| Torres, Arch Soc Esp Oftalmol 2008 (104)<br>N=58 CLAU | 21% | 100%/0% | 81%<br>Success defined by the absence of a persistence corneal epithelial defect, on-going inflammation or recurrence of a pterygium | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| **CLAL/KLAL** | | | | | | | | | |
| Burcu, Cutaneous Ocular Toxicol 2014 (35)<br>N=3 Lr-CLAL | 100% | 100%/0% | 100% lr-CLAL<br>50% KLAL | 56% (95% CI: 33% to 77%) for total population<br>Not given for subgroups | Not reported | Not reported | Not reported | Not reported | Not reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| N=2 KLAL | | | | | | | | | |
| Eslani, AAO 2015 (93)<br>N=5<br>KLAL | 60% | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Mean time to graft rejection 52 months |
| Gomes, Ophthalmol 2003 (47)<br>N=10 Lr-CLAL | 100% | 0%/100% | 60.0% (95% CI: 31.3% to 83.2%) | 87.5% (95% CI: 64.0% to 96.5%)<br>total population (not broken out by subgroups) | Not reported | Not reported | Not reported | Not reported | Reconstruction failed in three cases (75%) in the first 6 months and in one (25%) >1 year after the surgery. One of these three subjects in whom treatment failed in the first 6 months presented with graft necrosis on the eighth day after the surgery. The other two patients had |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | severe dry eye with keratinisation.<br>Systemic AEs with the use of immunosuppression were not observed in any case |
| Han, Graefe's Arch Clin Exp Ophthalmol 2011 (60)<br>N=22<br>KLAL | 32% | 90%/10% | 33%<br>Absence of persistent corneal epithelial defect, corneal conjunctivalisation, or NV on the corneal edge of the graft | 27% | Not reported | Not reported | Not reported | Not reported | Graft failure in 42% (87% reversed). Raised IOP was reported in 33% of patients, epithelial defect in 42% of patients and symblepharon in 18% of patients |
| Holland, Trans Am Ophthalmol Soc 1996 (94)<br>N=21 | 38% | 0%/100% | 72%<br>Stable ocular surface without epithelial | 60% | | | | | 54% rejection |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| KLAL | | | defects | | | | | | |
| Huang, Arch Ophthalmology 2011 (58)<br>N=17<br>Lr-CLAL | 100% | 29%/71% | Not reported | 100% (95% CI: 82% to 100%) | Not reported | Not reported | 59% | 100%<br>Corneal re-epithelialisation | Allograft rejection in 18% of eyes |
| Ilari, Ophthalmology 2002 (95)<br>N=20<br>KLAL | 40% | 85%/15% | 21%<br>Restored phenotypic corneal epithelium | 44% | Not reported | Not reported | Not reported | 76% | Graft failure 46% at 1 year, 67% at 2 years and 73% at 3 years. Raised IOP was reported in 26% of patients, and corneal necrosis and microbial keratitis each in 13% of patients |
| Maruyama-Hosoi, Cornea 2006 (96)<br>N=78 | 22% | 0%/100% | 55% (41% in ocular burns patients)<br>Successful ocular surface | Not reported | Not reported | Not reported | Not reported | Not reported | 13% rejection, 33% raised IOP, 8% infections, 4% corneal |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| KLAL | | | reconstruction defined as central corneal epithelialisation | | | | | | perforation and 2.5% retinal detachment |
| Miri, Ophthalmology 2010 (46)<br>N=15<br>Lr-CLAL and CLAL-CD | 50%<br>(Total population) | 0%/100% | 89% for lr-CLAL<br>33% for KLAL<br>Success measured by duration for which a healthy corneal epithelium was maintained after LSCT | 89% for lr-CLAL<br>33% for KLAL | Not reported | Not reported | Not reported | Not reported | Not reported |
| Solomon, Ophthalmol 2002 (102)<br>N=31<br>KLAL + AMT | 41% (16 eyes out of 39 eyes) | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | 10/39 eyes (25.6%) developed raised IOP, 14 eyes (35.9%) developed persistent epithelial defects. 3 eyes developed microbial keratitis |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tan, Ophthalmology 1996 (103)<br>N=9<br>Lr-CLAL and CLAL-CD | 11% | 0%/100% | 78% | 44% | 33% | Not reported | 77.8% | Not reported | A range of adverse events reported in 77.8%, including cataract, glaucoma, spastic entropion, keratitis, infection and acute rejection after stopping cyclosporine |
| Titiyal, Ocular Immunol Inflamm 2015 (42)<br>N=10 Lr-CLAL<br>N=10 KLAL | 100% | 100%/0% | 100% (95% CI: 84% to 100%) | 80% lr-CLAL (n=10)<br>50% KLAL (n=10)<br>Overall 65% (95% CI: 43% to 82%) | Not reported | Not reported | 80% CLAL<br>50% KLAL | Not reported | There were no intraoperative complications, such as damage to muscle during symblepharon release or corneal perforation. Up to the minimum follow-up period of 6 months none |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | of the eyes in either group developed any infection or necrosis of cornea |
| Torres, Arch Soc Esp Oftalmol 2008 (104)<br>N=14<br>CLAL-CD | 43% | 0%/100% | 7%<br>Success defined by the absence of a persistence corneal epithelial defect, on-going inflammation or recurrence of a pterygium | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| Tsai, Cornea 1994 (97)<br>N=16<br>CLAL-CD | 31% | 0%/100% | 63%<br>Surface healing | 81% | Not reported | Not reported | 75% | Not reported | No graft failure |
| Tsubota, Ophthalmology 1995 (98) | 33% | 0%/100% | 56%<br>Stable corneal epithelium | 100% | Not reported | Not reported | Not reported | Not reported | Aphakia was reported in 56% of patients, |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| N=9<br><br>CLAL-CD | | | | | | | | | bullous keratopathy in 67% of patients, and glaucoma and cataract each in 30% of patients |

### 4.11.6 Summary of non-randomised and non-controlled evidence

*Ocular stability*

For the publications reporting the number/percentage of patients who achieved OS, there was evidence of significant heterogeneity across studies in terms of outcome and patient population. Therefore no pooling of results from these studies has been carried out due to the significant differing characteristics of the study designs. Overall, patient population size ranged from 5 to 152, with the three largest studies for Holoclar.

Of the 11 studies providing data on CLAU, only 5 studies were conducted exclusively in patients with ocular burns.(35,47,55,92,100) In the remaining 6 studies, the proportion of patients with ocular burns varied from 21% to 85%.(46,90,91,101,103,104) Separate results were not reported for ocular burn patients, although the Dua(90) and Miri(46) studies noted 100% of all patients achieving OS. Of the 15 studies providing data on CLAL/KLAL, only 4 studies were exclusively in patients with ocular burns.(35,42,47,58) In the remaining 11 studies, the proportion of patients with ocular burns varied from 11% to 60%.(46,60,93–98,102–104) With the exception of Maruyama-Hosoi,(96) separate results were not reported for ocular burn patients.

Success rates were available for 4 of the 5 studies providing data on CLAU in patients with ocular burns. The success rates were 14/16 (87.5%) [or 14/21 (66.7%) with cases requiring a second transplantation taken into account], 5/6 (83.3%), 15/16 (94%) and 6/6 (100%).(35,47,55,100) Only three of the studies providing data on CLAL/KLAL conducted exclusively in ocular burns patients reported success rates. The success rates were 4/5 (80%), 20/20 (100%) and 6/10 (60%).(35,42,47) Additionally, in the Maruyama-Hosoi study, success was seen in 41% of the ocular burns patients.(96)

Of the 7 Holoclar studies, 3 were conducted exclusively in ocular burn patients(78,81,83) and the outcomes for ocular burn patients could be calculated for 2 others.(7,8) For these five studies, the percentages of ocular burn patients achieving OS were 62.6% (n=16), 78% (n=18), 67.3% (n=112), 74.5% (n=104) and 60% (n=15) respectively.(7,8,78,81,83) The patient populations of Rama 2010 and

HLSTM01 have significant overlap; so the two were not used together for the analysis of pooled success rate. Pooling the success rates for initial treatment, the overall success rate for patients with ocular burns treated with Holoclar was 67.3% (95% CI: 59.5% to 74.3%).

*Visual acuity*

For the publications reporting the number/percentage of patients who achieved improvement in VA, there was also evidence of significant heterogeneity across studies in terms of outcome and patient population. Methods of assessing improvements in VA also differed between studies. Therefore no pooling of results from these studies has been carried out due to the significant differing characteristics of the study designs. Overall, patient population size ranged from 5 to 152, with the three largest studies for Holoclar.

Again, of the 11 studies providing data on CLAU, only 5 studies were conducted exclusively in patients with ocular burns.(35,47,55,92,100) In the remaining 6 studies, the proportion of patients with ocular burns varied from 21% to 85%.(46,90,91,101,103,104) Of the 15 studies providing data on CLAL/KLAL, only 4 studies were exclusively in patients with ocular burns.(35,42,47,58) In the remaining 11 studies, the proportion of patients with ocular burns varied from 11% to 60%.(46,60,93–98,102–104)

In studies investigating CLAU or CLAL/KLAL exclusively in patients with moderate to severe LSCD due to ocular burns where VA was assessed, there was a broad range of VA outcomes reported (20% to 100% of patients with improvement in VA for CLAU(35,47,55,92,100) and 65-100% for CLAL/KLAL(42,47,58). In the 4 studies providing VA data on CLAU, improvement in VA was seen in 6/6 (100%), 9/13 (69%), 1/5 (20%), and 10/10 (100%).(47,55,92,100) In the 3 studies providing VA data on CLAL/KLAL, improvement in VA was seen in 13/20 (65%), 8/10 (80%) and 17/17 (100%).(42,47,58)

Of the 3 Holoclar studies conducted exclusively in ocular burn patients where VA was assessed (n=49), the percentage of patients with improvement in VA ranged from 40-71.4%.(78,81,83) In HLSTM04, improvement in VA was seen in 40% of the

patients with stromal scarring.(83) In the published studies by Marchini and Rama 2001, the values were and 46.2% and 71.4%, respectively.(78,81)

## *4.12 Adverse reactions*

There is no evidence from RCTs to inform as to the safety profile of Holoclar or any of the comparator technologies. However, a range of adverse events have been reported in the studies presented in the tables in Section 4.11. These are summarised below.

### 4.12.1 Adverse events associated with Holoclar

In HLSTM01, 6 serious AEs (3 were fatal) were reported after 6 transplantation procedures (5.3%), all in subjects with one transplantation (5.9%).35 None of them was considered as treatment-related. A total of 22 ADRs were reported after 19 transplantation procedures (16.8%). There were no ADRs potentially related to antibiotics up to one month after transplantation. AEs potentially related to corticosteroids (occurring up to 3 months after transplantation) were reported in 6 cases (5.3%), 5 consisted of glaucoma and 1 of gastritis. Only one case of glaucoma was considered by the investigator as treatment-related (i.e. as ADR).

In HLSTM02, a total of 46 AEs were reported in 19 treatments (65.5%).36 Of these, 21 events occurring in 10 treatments (34.5%) were judged as ADRs. Eye disorders were the most common group of AEs observed, with eye pain (17.2%) and glaucoma (13.8%) as the most common single AEs reported. Corneal graft (keratoplasty) rejection was reported in 2 cases (6.9%). Another patient had other graft complications. One case of corneal infection after transplantation was reported. Five SAEs were reported in 3 treatments (10.3%) and 10 AEs of severe intensity were reported in 6 treatments (20.7%). Three SAEs in 2 patients were considered treatment-induced: vasovagal syncope in 1 patient, and ulcerative keratitis and corneal perforation in the other. None of the AEs led to study withdrawal.

In HLSTM04, 60% of patients experienced AEs (14 AEs), the most frequent being eye disorders and nervous systems disorders.37 Only one SAE was reported and characterised as not related to the procedure (stroke).

As with all medicinal products to be granted a Marketing Authorisation, the current approved SmPC for Holoclar contains the full and most up-to-date information on the safety profile of Holoclar. Adverse reactions reported in patients implanted with Holoclar are provided in table 15 below.

**Tale 15: Adverse reactions for Holoclar by frequency of occurrence**(6)

| System/Organ Class | Adverse Reaction | Frequency |
|---|---|---|
| Infectious and infestations | Corneal infection | Uncommon (≥1/1,000 to <1/100) |
| Nervous system disorders | Syncope vasovagal | Uncommon (≥1/1,000 to <1/100) |
| Eye disorders | Blepharitis | Very common (≥1/10) |
| | Conjunctival haemorrhage, eye haemorrhage, corneal epithelium defect, eye pain, glaucoma/intraocular pressure increased, ulcerative keratitis | Common (≥1/100 to <1/10) |
| | Conjunctival adhesion, conjunctival hyperaemia, corneal oedema, corneal perforation, eye irritation, photophobia | Uncommon (≥1/1,000 to <1/100) |
| Skin and subcutaneous tissue disorders | Haemorrhage subcutaneous | Uncommon (≥1/1,000 to <1/100) |
| General disorders and administration site conditions | Metaplasia of the implant | Uncommon (≥1/1,000 to <1/100) |
| Injury, poisoning and procedural complications | Suture rupture | Uncommon (≥1/1,000 to <1/100) |

The most common adverse reactions seen with Holoclar are eye disorders. The most frequently occurring reaction related to the surgical procedure was conjunctival haemorrhage (5%) which appears mostly during the first day after surgery and tends to be mild in intensity and disappears within a few days without treatment. Blepharitis (10.5%), and corneal epithelium defect (3.5%) were the most common individual adverse reactions not related to the surgical procedure.(6)

The most serious adverse reactions are corneal perforation and ulcerative keratitis, which may occur within the 3 months from Holoclar implantation and are related to the corneal epithelial instability, and syncope vasovagal occurring in the first day

after surgery due to eye pain. Glaucoma (3.5%) was the most frequent adverse reaction considered related to the corticosteroid treatment. Reports of glaucoma included adverse reactions of intraocular pressure.(6)

Further information regarding the safety profile of Holoclar can be found in the Holoclar summary of product characteristics, see Appendix 1.

### 4.12.2 Adverse events associated with comparator technologies

*CLAU*

AEs were reported in 5 studies providing data on CLAU and an adverse effect on the donor eye was reported in 2 studies. These findings are described in table 16 below.

**Table 16: Adverse events associated with CLAU**

| Study | Adverse events |
|---|---|
| Dua, Br J Ophthalmol 2000 (90) N=6 CLAU | No intraoperative complications, infection or graft failure were reported.11 Postoperatively keratitis occurred in 17% of patients and one patient developed filamentary keratitis along the edge of the donor site. |
| Ivekovic, Ophthalmologica 2005 (100) N=6 CLAU N=4 CLAU+ AMT | No infection, limbal graft failure or slippage of tissue was reported.15 In this study, there were no intraoperative complications, refractive changes or corneal NV in any of the donor eyes. |
| Kenyon, Ophthalmology 1989 (91) N=26 CLAU | No intraoperative complications, infections or graft failure were reported. |
| Meallet, Ophthalmol 2003 (101) N=5 CLAU + AMT | A transient epithelial defect in one eye and migration of pigmented epithelium onto the AMT-covered limbus in another eye was reported. |
| Tan, Ophthalmology 1996 (103) N=9 CLAU | CLAU failure occurred in two patients (who had chronic contact lens-associated epitheliopathy).One contact lens wearer had epithelial dysplasia in the fellow eye at the previous donor site. Subclinical involvement of the fellow eye is suggested as a reason for graft failure and donor eye complications in these eyes. |

Given the study designs, retrospective nature and incomplete reporting of safety information for all patients included in these case series, it is not possible to give relative risk and risk differences associated with these adverse events.

Expert opinion(57) suggests that in clinical practice in England, primary failure of engraftment occurs in around 10%, and of those that fail to engraft, 50% of patients will experience a persistent epithelial defect. Infection, mainly bacterial (or fungal) occurs in 0-20% of grafted eyes and 0 to <5% of donor eyes. Glaucoma secondary to topical steroids treatment post-CLAU is seen in 5-10%. Failure of CLAU and recurrence of LSCD seen in 20-30% by 10 years.

*CLAL/KLAL*

Adverse events were reported in 12 studies providing data on CLAL/KLAL and, for lr-CLAL, an adverse effect on the donor eye was reported in none of these studies. These findings are described in table 17 below.

**Table 17: Adverse events associated with CLAL/KLAL**

| **Study** | **Adverse event** |
|---|---|
| Eslani, AAO 2015 (93)<br>N=5 KLAL | Mean time to graft rejection 52 months |
| Gomes, Ophthalmol 2003 (47)<br>N=10 Lr-CLAL | Reconstruction failed in three cases (75%) in the first 6 months and in one (25%) >1 year after the surgery. One of these three subjects in whom treatment failed in the first 6 months presented with graft necrosis on the eighth day after the surgery. The other two patients had severe dry eye with keratinisation.<br>Systemic AEs with the use of immunosuppression were not observed in any case. |
| Han, Graefe's Arch Clin Exp Ophthalmol 2011 (60)<br>N=22 KLAL | Graft failure in 42% (87% reversed). Raised IOP was reported in 33% of patients, epithelial defect in 42% of patients and symblepharon in 18% of patients. |
| Holland, Trans Am Ophthalmol Soc 1996 (94)<br>N=21 KLAL | 54% rejection. |
| Huang, Arch Ophthalmology 2011 (58)<br>N=17 Lr-CLAL | Allograft rejection in 18% of eyes. |

| | |
|---|---|
| Ilari, Ophthalmology 2002 (95)<br>N=20 KLAL | Graft failure 46% at 1 year, 67% at 2 years and 73% at 3 years. Raised IOP was reported in 26% of patients, and corneal necrosis and microbial keratitis each in 13% of patients. |
| Maruyama-Hosoi, Cornea 2006 (96)<br>N=78 KLAL | 13% rejection, 33% raised IOP, 8% infections, 4% corneal perforation and 2.5% retinal detachment. |
| Solomon, Ophthalmol 2002 (102)<br>N=31 KLAL + AMT | 10/39 eyes (25.6%) developed raised IOP, 14 eyes (35.9%) developed persistent epithelial defects. 3 eyes developed microbial keratitis. |
| Tan, Ophthalmology 1996 (103)<br>N=9 Lr-CLAL and CLAL-CD | A range of adverse events reported in 77.8%, including cataract, glaucoma, spastic entropion, keratitis, infection and acute rejection after stopping cyclosporine. |
| Titiyal, Ocular Immunol Inflamm 2015 (42)<br>N=10 Lr-CLAL<br>N=10 KLAL | There were no intraoperative complications, such as damage to muscle during symblepharon release or corneal perforation. Up to the minimum follow-up period of 6 months none of the eyes in either group developed any infection or necrosis of cornea. |
| Tsai, Cornea 1994<br>N=16 (97)<br>CLAL-CD | No graft failure. |
| Tsubota, Ophthalmology 1995 (98)<br>N=9 CLAL-CD | Aphakia was reported in 56% of patients, bullous keratopathy in 67% of patients, and glaucoma and cataract each in 30% of patients. |

Given the study designs, retrospective nature and incomplete reporting of safety information for all patients included in these case series, it is not possible to give relative risk and risk differences associated with these adverse events.

Expert opinion(57) suggests that in clinical practice in England, primary failure of engraftment occurs in around 20% of patients, and of those that fail to engraft, 50% will experience a persistent epithelial defect. Infection, mainly bacterial (or fungal) occurs in 0-20% of grafted eyes and 0 to <5% of donor eyes for lr-CLAL. Glaucoma secondary to topical and systemic post-operative immunosuppression is seen in 10%. Failure of CLAL/KLAL and recurrence of LSCD seen in 100% by 3-5 years.

*Best supportive care*

Adverse events were not reported in any of the studies providing data on best supportive care.

Expert opinion(57) suggests that in clinical practice in England, patients treated with best supportive care are likely to experience inflammatory flare-ups and failure of treatment resulting in recurring epithelial defects. It is estimated that 90% of patients experience this at least once per year and 50% twice per year. Some patients may experience as many as 3 flares per year. Microbial keratitis occurs in 5% of patients at least once per year and 10-20% of patients treated with best supportive care require surgical intervention or hospitalisation for treatment of infection or persistent epithelial defect each year. Hospital admission is required to treat both of these adverse events and typically 5-7 days (up to 14 days) hospital admission is required. Glaucoma from steroid use is seen in 10% of patients treated with best supportive case if steroids are used chronically.

## *4.13 Interpretation of clinical effectiveness and safety evidence*

### 4.13.1 Principal findings from the clinical evidence

*Beneficial effects of Holoclar*

The therapeutic approach of using autologous ex-vivo expanded limbal stem cells for treatment of LSCD offers several advantages compared to alternative methods for ocular surface reconstruction, such as limbal allografts with an associated risk of rejection requiring long-term systemic immunosuppression, or non-expanded limbal autografts from the healthy fellow eye which may lead to iatrogenic induction of LSCD in the donor eye. Successful reconstruction treatment is reflected by the restoration of a stable corneal epithelium with resolution of epithelial defects, regression of corneal vascularisation, and absence of conjunctivalisation. If treatment with Holoclar is successful at 12 months postoperatively, then it is likely to remain successful over at least the next 10 years, i.e. the longest time period for which survival analysis has been conducted.

For Holoclar transplants, treatment success has been shown in retrospective analyses of a total of 133 patients receiving 142 transplantation during 1998 to 2007 (7,82) with additional supportive data provided for 15 patients treated from 2008 to 2013.(83) Overall, in the pivotal study HLSTM01(7), 72% (75/104) of all analysed patients were considered a treatment success based on achievement of a stable corneal epithelium without significant recurrence of neovascularisation 12 months

after surgery. Long-term data up to 10 years, although limited, suggested persistence of the effect. Overall, this was a convincing outcome considering that LSCD would not be expected to improve spontaneously.

Clinically meaningful outcomes for LSCD patients were furthermore the improvements of ocular symptoms and visual acuity. Most of the patients showed a stable clinical picture at baseline, and only a limited number had ocular symptoms (pain, photophobia, burning, bulbar or limbal hyperaemia). Treatment with Holoclar maintained the stable clinical picture or resulted in an improvement and/or resolution of manifestations as shown by a reduction of the number of patients with symptoms as well as a decrease in the intensity of ocular pain, burning, and photophobia. In addition, clinically relevant improvement of visual acuity of 3 lines on the vision chart was observed in 38.5% (40/104) of the patients and half of the patient with off-chart vision at baseline gained on-chart vision after Holoclar treatment.

Unsurprisingly, improvements in vision were achieved in more patients without stromal scarring compared to those with deep stromal injury. However, within the latter group of patients, vision improved to a similar extent with a 3 line gain in VA seen in 37.5% (21/56) of patients after corneal transplantation. It was furthermore found that Holoclar treatment increased the chance for subsequent successful keratoplasty, which was another therapeutically meaningful achievement in the group of patients with deep stromal scarring. Post-Holoclar keratoplasty was successful in 42% (24/57) of patients as well as in half of all patients who had a failed corneal transplantation prior to Holoclar.

*Unfavourable effects of Holoclar*

Eye-related disorders were the most commonly observed adverse events occurring in 57% of the safety population. The most commonly experienced ADRs were conjunctival haemorrhage, corneal epithelial defects consistent with treatment failure, eye pain and haemorrhage, and blepharitis.

The overall rate of serious ADRs with three cases in the entire study population was regarded as low. However, an imbalance in the reporting rates of adverse events and reactions was observed between studies. Far less adverse events occurred in study HLMST01(7) involving two experienced clinical sites, compared to other

centres with less practice, analysed in study HLMST02(82) or reported by Marchini et al.(78) Therefore, measures to ensure adequate and comparable levels of training across treatment centres are required and have been put in place for the UK.

Several adverse effects were related to the surgical intervention including conjunctival haemorrhage. The risk of local ocular inflammation or infection was mitigated by a prophylactic anti-inflammatory and antibiotic regimen combining both topical non-cytotoxic and systemic treatments. However, these concomitant treatments may cause adverse reactions themselves. In this context, the observed events of glaucoma that occurred within 3 months of Holoclar were considered related to the use corticosteroids.

*Comparative evidence for Holoclar, CLAU, CLAL and KLA*L

Systematic literature reviews have identified no RCTs directly comparing these technologies. Due to the nature of the available data, i.e. retrospective, observational case series often with small numbers of patients and with short follow-up periods, it is not possible to formally compare, either directly or indirectly, the alternative technologies.

Whilst the pivotal trial for Holoclar, HLSTM01,(7) is also observational in nature it has a relatively large sample size followed over a long period of time (maximum 10 years). This leads to a slightly unusual situation in which there is substantially more robust evidence regarding the new technology, Holoclar, than there is regarding the identified established comparators. Nevertheless the nature of the evidence base makes it difficult to produce definitive conclusions either for individual technologies or across the different treatment modalities.

*Benefit-risk balance*

Treatment with Holoclar resulted in the majority of patients in a successful OS reconstruction, maintaining a stable clinical picture or resulting in an improvement and/or resolution of LSCD manifestations, including symptoms and VA. The improvement of ocular symptoms was a relevant clinical outcome in particular for patients with moderate LSCD, where a small structural improvement by itself would be of limited clinical relevance. Furthermore, clinically relevant vision gains were

achieved in a subset of patients including regaining of on-chart vision, which is of relevance in a population where the majority of patients are legally blind. Clinically relevant outcomes were observed both in patients with and without deep stromal injury. Furthermore, Holoclar was shown to increase the likelihood for a successful subsequent keratoplasty in patients with deep stromal scarring. Albeit data were collected retrospectively and uncontrolled, these results were highly clinically relevant considering that moderate to severe LSCD is a condition that would not improve spontaneously. In this context, Holoclar addresses an unmet medical need considering that no treatments for LSCD had been approved for marketing in the EU at the time of this report. Furthermore, Holoclar should be considered advantageous compared to alternative, allogeneic treatment methods, requiring systemic immunosuppression.

Eye-related disorders were the most commonly observed adverse events, with the most commonly experienced adverse reactions comprising conjunctival haemorrhage, corneal epithelial defects consistent with treatment failure, eye pain and haemorrhage, and blepharitis. The majority of the adverse effects were manageable and the overall safety profile of the Holoclar treatment procedure can be regarded acceptable and generally well-tolerated.

In conclusion, the benefit-risk balance for Holoclar in the treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus for biopsy, should be considered favourable. This view is supported by the grant of a Marketing Authorisation for Holoclar on 17$^{th}$ February 2015, and the conditional nature of the Marketing Authorisation reflects the Regulatory Authority's desire to make Holoclar available within the European due to significant unmet clinical need in this population.

### 4.13.2 Internal and external validity

The internal validity of the studies for CLAU, CLAL and KLAL is compromised in several ways. There is no accepted standard endpoint to determine success or

failure of the procedure and no agreement regarding the time point at which this is measured. Consequently, the endpoints used in the studies of CLAU, CLAL and KLAL are different from case series to case series. Assessment bias may further compromise the internal validity of these studies. Rather than an objective measure of the true effects of the outcome being used, many of the key endpoints of the studies are subjective, e.g. success being defined in the opinion of the surgeon who performed the procedure following slit lamp examination only and without quantified impression cytology. Furthermore, the effects on visual acuity are rarely and poorly documented, yet this is an important outcome for patients.

The external validity of the studies for CLAU, CLAL and KLAL is additionally compromised. In many cases, inclusion/exclusion criteria are not confined to moderate to severe LSCD due to physical or chemical burns therefore the ability to extrapolate the results to this specific population is limited. The surgical nature of the procedure also compromises external validity, i.e. different surgeons are likely to have different individual techniques and post-operative care regimens and therefore reproducibility of the reported outcomes in different treatment centres cannot be guaranteed. Reporting bias may further compromise the external validity of the evidence base for CLAU, CLAL and KLAL as it is unlikely that surgeons will be motivated to write up case series of failed surgical procedures (or indeed that this would have been published).

In contrast, to support the internal validity of the Holoclar study HLSTM01,(7) the criteria for success for Holoclar were pre-defined and are as used in clinical practice to assess treatment outcomes; the same surgical procedure was followed for all patients, ensuring consistency in delivery; similar post-surgical management was provided for all patients, including antibiotic and anti-inflammatory therapy; and there was availability of photographic records of the affected eye for most patients, which provided objective evidence of the effect thus reducing the element of assessment bias associated with these data. In addition, data were objectively re-evaluated in a blinded fashion by an independent assessor and the potential sources of biases in the data collection were investigated and whether this could significantly influence the benefit-risk of the product was assessed.

To address the impact on internal validity due to distortions or mistakes in the collection of information, the system for data collection, traceability and analysis for the Holoclar trials followed the ICH-E6 Guideline in Good Clinical Practice.(107) The clinical study protocols and a data management system were defined *a priori* before starting data collection at the clinical sites. A consistent approach to data collection and analysis/review was applied (including training of investigators) and a clinical contract research organisation was appointed for data source verification. A Statistical Analysis Plan was also prepared for each study before database lock.

The effect on the external validity of the Holoclar studies of missing data due to the inability to include all patients previously treated with Holoclar due to consent issues, was also assessed by comparing the results seen in HLSTM01(7) with the findings from published literature (which also included 25/82 of the remaining patients treated with Holoclar). An extensive analysis of missing data (including several sensitivity tests) revealed that the degree of this potential issue was minimal and had virtually no impact on the overall results. Therefore the ability to extrapolate the findings of the Holoclar studies to the wider clinical setting can be justified.

### 4.13.3 End of life criteria

Life expectancy is discussed in section 3.4. Given the rarity of moderate to severe LSCD due to ocular burns,(3) there is no specific data available for the impact of this condition on life expectancy. However, regional and global average life expectancies and health life expectancy at birth for 2015 have been reported by the WHO.(68) These data suggest that there is a gap between life expectancy and health life expectancy due to visual loss.

**Table 18: End-of-life criteria**

| Criterion | Data available |
|---|---|
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | Not applicable |
| There is sufficient evidence to indicate that the treatment offers an extension to life, | Not applicable |

| | |
|---|---|
| normally of at least an additional 3 months, compared with current NHS treatment | |
| The treatment is licensed or otherwise indicated for small patient populations | Maximum estimate of prevalent cases of LSCD due to physical and chemical ocular burns in England = 121 patients. In addition, the estimated incidence of new cases of severe chemical corneal injury is 0.02 in 100,000 people, i.e. 13 new cases per year.(36)<br>See section 3.4.1. |

## *4.14 Ongoing studies*

There are no completed or ongoing studies from which additional evidence is likely to be available in the next 12 months for the treatment of adult moderate to severe LSCD due to ocular burns. However, Chiesi are conducting three further phase IV studies with Autologous Cultivated Limbal Stem Cells Transplantation (ACLSCT), i.e. Holoclar, in patients with LSCD due to ocular burns.

*HOLOCORE*(12)

Clinical trial HLSTM03 (HOLOCORE) is a European, multinational (eight countries), multicentre, prospective, open-label, uncontrolled clinical trial of Holoclar in adult and paediatric patients with moderate to severe unilateral or bilateral LSCD due ocular burns. Target patient numbers include 87 adults and 5 children/adolescents aged 2-17 years.

In adult patients, the primary objective is to demonstrate the efficacy of Holoclar at one year after the first treatment in patients suffering from moderate to severe (at least two corneal quadrants, central corneal involvement resulting in severe visual impairment) LSCD secondary to ocular burns. The key secondary objective is to evaluate the efficacy of one or two treatments with Holoclar at one year after the last treatment. Other secondary objectives include:

- to evaluate the degree of corneal re-epithelialisation during follow-up;
- to evaluate the degree of severity of superficial corneal neovascularisation during follow-up;
- to evaluate the improvement in the presence and severity of clinical symptoms (pain, burning and photophobia) after last treatment with Holoclar during follow up;
- to evaluate the presence and severity of limbal and bulbar inflammation after last treatment with Holoclar during follow up;
- to evaluate the improvement in best corrected visual acuity after last treatment with Holoclar during follow up;
- to evaluate the improvement in patient's quality of life after last treatment with Holoclar during follow up;
- to evaluate the success of ACLSCT (Autologous Cultivated Limbal Stem Cells Transplantation) by number of Holoclar applications (either one or two); and
- to evaluate the clinical safety profile of ACLSCT, including limbal biopsy, Holoclar transplantation procedure and post-transplantation treatment.

Additional exploratory objectives are to evaluate the mean change from baseline in tear secretion by Schirmer's test type I 12-month after last treatment with Holoclar; to evaluate success of treatment according to investigator's judgment; and to evaluate the stability of the disease during the roll-in period (as per corneal neovascularisation, epithelial defect, limbal and bulbar hyperaemia, symptoms and visual acuity).

For the paediatric patients included in this study, the objectives are to evaluate the clinical safety profile of treatment with ACLSCT (including limbal biopsy, Holoclar, transplantation procedure and post-transplantation treatment) and to explore the following efficacy parameters:

- presence of pain, burn and photophobia after the last treatment with Holoclar during follow-up;
- presence of limbal and bulbar inflammation after the last treatment with Holoclar during follow-up;
- degree of severity of superficial corneal neovascularisation and (if tolerated) of epithelial defects during follow up;
- improvement in best corrected visual acuity after the last treatment with Holoclar during follow up; and
- improvement in patient's quality of life after last treatment with Holoclar during follow up.

Results from this study are expected in 2020 and it is anticipated that this will provide prospective confirmation of the previously observed efficacy and safety results from the retrospective evaluation studies previously discussed (i.e. HLSTM01, HLSTM02 and HLSTM04), as well as forming the basis for an extension of the indication for Holoclar in paediatric patients aged 2-17 years.

*HOLOCORE-FU*(13)

Clinical trial HLSTM03-FU (HOLOCORE-FU) is a multinational, multicentre, prospective, long-term safety and efficacy follow-up study after Holoclar for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns.

The primary objective is to demonstrate the long term safety of one or two Holoclar treatments in patients suffering from moderate to severe LSCD secondary to ocular burns. Secondary Objectives include:

- to evaluate the long-term efficacy of one or two ACLSCT(s), the degree of superficial corneal neo-vascularisation and corneal epithelial stability, clinical symptoms, conjunctival inflammation, visual acuity, quality of life compared to baseline (i.e. before the first Holoclar) and long-term efficacy based on clinical judgment of the investigator.

- to evaluate safety and clinical outcomes (i.e. superficial corneal neo-vascularisation, epithelial defects, visual acuity, conjunctival inflammation, and symptoms) after keratoplasty in patients previously treated with Holoclar.

Patients will enter this study as they complete the 12 months of follow-up for the main HOLOCORE study (see above). No further by-protocol treatment is planned. During the HOLOCORE-FU study, patients will undergo study visits every 6 months and at the time of study closure (i.e. at an “end-of-study visit” when the last patient rolling over from HOLOCORE will have reached 12 months of observation). Safety and efficacy data will be collected at each study visit.

Individual patient duration for HOLOCORE-FU will vary from a minimum duration of 12 months, for the last patient entered, to up to potentially 49 months for the first enrolled patient.

*HOLOSIGHT*(14)

Clinical trial HLSTM05 (HOLOSIGHT) is a non-interventional, observational, multinational, multicentre, prospective cohort study of Holoclar to be conducted in all European countries where Holoclar is used. This is a registry study required as part of the agreed Risk Management Plan (RMP) for Holoclar. The primary objective of this study is to evaluate the long-term safety profile of patients treated with Holoclar during a 5-year follow-up period from first ocular implantation under routine clinical conditions, through the description of the occurrence of adverse events, adverse drug reactions, serious adverse events and adverse events of special interest. Adverse events identified of special interest will be solicited and carefully monitored. Secondary aims and objectives include:

- to describe demographic and clinical characteristics of patients undergoing one or more Holoclar implants including the occurrence of ocular grafts preceding the investigated implant;

- to describe the proportion of success, according to clinician’s judgment, one year after implant, among patients undergoing one or more Holoclar® implants;

- to describe visual acuity during a 5-year follow-up from first implant;
- to describe quality of life, as measured by EuroQol-Five Dimensions (EQ-5D) and National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25), during a 5-year follow-up from first implant;
- to describe the administered post-implant surgical treatment, including keratoplasty; and
- to evaluate the effectiveness of the risk minimisation measures in compliance with the RMP for Holoclar.

The overall study duration is anticipated to be 7-9 years and analyses will be conducted and reported periodically to the relevant Regulatory authorities. These results will be used to add to the safety database for Holoclar and to examine the long-term safety and efficacy of Holoclar in routine clinical use.

# 5 Cost effectiveness

## *5.1 Published cost-effectiveness studies*

A systematic literature search was conducted to identify and select relevant studies examining the clinical effectiveness, safety and impact on HRQoL of Holoclar and comparator technologies. In line with standard methodology, multiple databases were used:

- Embase
- Medline (through PubMed)
- Cochrane Library:
    a. Cochrane Database of Systematic Reviews (Cochrane reviews)
    b. Database of Abstracts of Reviews of Effects (Other reviews)
    c. Cochrane Central Register of Controlled Trials (Clinical trials)
    d. Cochrane Methodology Register (Methods studies)
- EconLit

In order to identify relevant findings presented at international scientific conferences during the past 2 years that may not yet have been published in MEDLINE or EMBASE indexed peer-reviewed journals, the following “grey” literature sources (material that can be referenced, but is not necessarily published in peer-reviewed, MEDLINE or EMBASE indexed medical journals) were also manually searched for any relevant information. All of these sources are international scientific conferences:

- American Academy of Ophthalmology (AAO)
- European Association for Vision and Eye Research (EVER)
- European Society of Ophthalmology (ESO)
- Investigative ophthalmology & visual science (IOVS)

- The Royal College Of Ophthalmologists (RCO) Annual Congress
- World Congress of Ophthalmology (WCO)

The literature search included studies of human subjects published in English and non-English. The period covered by the literature search was January 1989 to January 2016 for published papers and January 2014 to January 2016 for conference material. The search strategies and search terms are included in the systematic review report for Holoclar, see Appendix 4.

Given that LSCD is a rare condition and, prior to Holoclar, no medical therapies have been available to treat this condition, it was expected than only a small number of studies would likely be identified. Therefore, the inclusion criteria were simplified to take this into account. The inclusion and exclusion criteria are set out below:

Inclusion criteria:

- Published in English and non-English
- Human population
- Patients with a confirmed diagnosis of LSCD

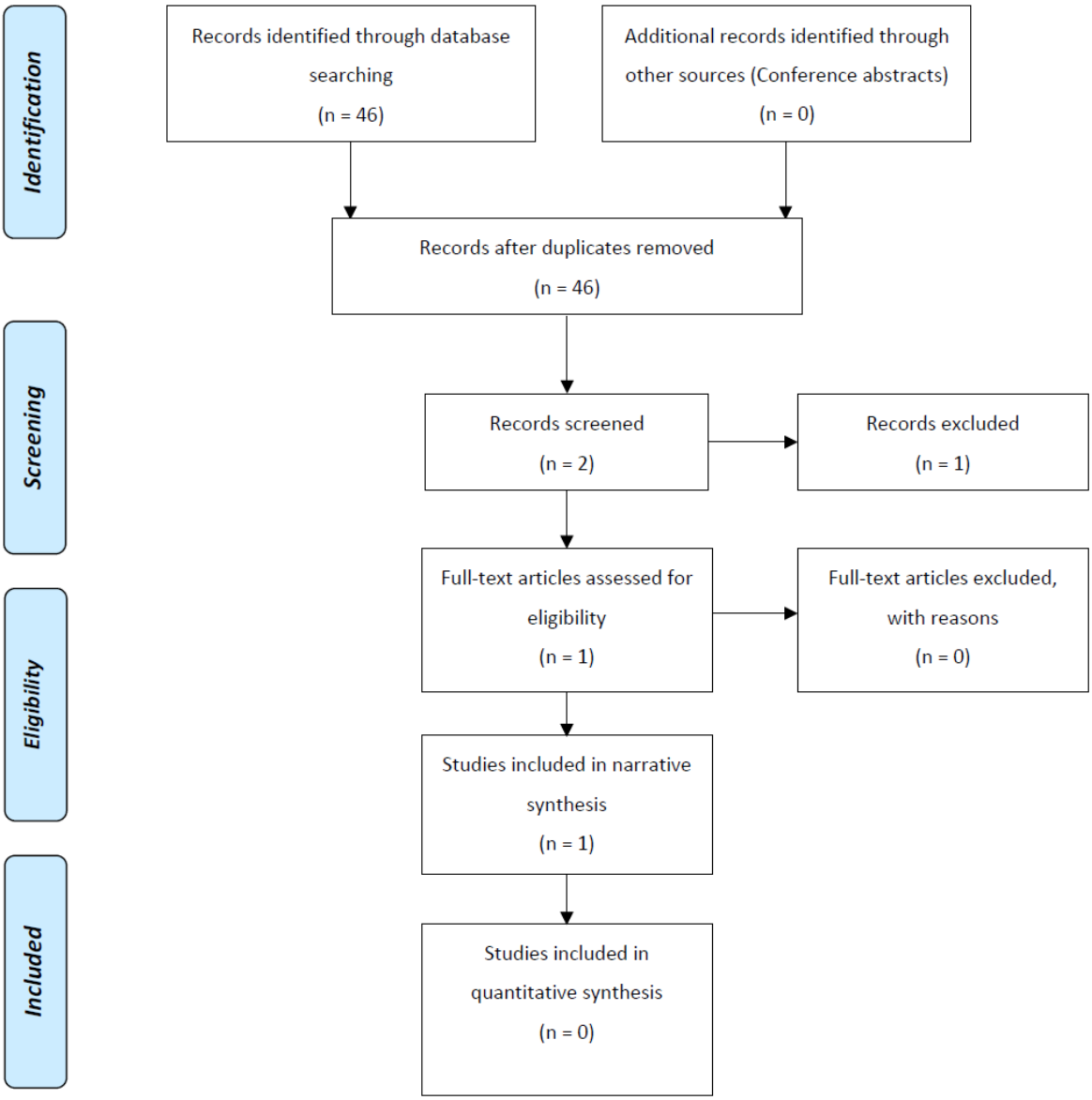
Exclusion criteria:

- Outside of scope, i.e. did not address the cost-effectiveness of CLAU, CLAL, KLAL or Holoclar
- Studies that were conducted in paediatric patients (aged <18 years)
- No cost-effectiveness data presented for CLAU, CLAL, KLAL or Holoclar

Two reviewers independently inspected each reference (title and abstract) identified by the literature search and applied the study selection criteria. For possibly relevant articles (i.e. where relevance is not clear), or in cases of disagreement between the two reviewers, the full article was obtained and inspected. Secondary assessment outlining the reasons for reference exclusion was provided.

A PRISMA flow diagram showing the numbers of studies included and excluded at each stage is provided below:

**Figure 13: PRISMA flow diagram of evidence for cost-effectiveness for Holoclar in the treatment of moderate to severe LSCD due to physical or chemical ocular burns**




For Holoclar, 1 study was identified by systematic literature search as relevant for inclusion in this technology appraisal. This study is described in table 19 below. No studies were excluded.

**Table 19: Published studies of Holoclar identified by the systematic literature search**

| Author, *Journal*, Year (Study name) | Study location, design, and duration | Intervention | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Fordham, Value in Health 2015 (108) | HLSTM01<br>UK, retrospective, case-series, non-randomised, non-controlled, multicentre clinical study | GPLSCD01 (n=99)<br>Conservative treatment (n=not given) | VA and symptoms (pain, burning and photophobia) to assess QoL and QALYs (Cost Effectiveness Analysis) | 10 years | Patients under conservative treatment had between 10.29 and 17.24 QALYs, depending on LSCD severity, whereas patients treated with GPLSCD01 showed between 15.93 and 22.49 QALYs, with a total utility gain between 5.25 and 6.04 QALYs in the GPLSCD01 group, this result being already discounted by 3.0%, in compliance with NICE guidelines.<br>Due to the utility gain, GPLSCD01 would meet NICE conventional ICER thresholds (20,000 – 30,000 GBP/QALY) up to a treatment cost of 150,000 GBP. |

There has been one analysis of cost-effectiveness of Holoclar relative to conservative treatment, presented in an abstract by Fordham et al.(108) Data were analysed and a total utility gain of between 5.25 and 6.04 QALYs in the Holoclar group relative to conservative treatment was reported, at a discounted rate of 3.0%, which would meet the NICE conventional ICER thresholds (20,000-30,000 GBP/QALY) up to a treatment cost of 150,000 GBP.

There are however a number of reservations about the economic model. In terms of the methodology used for discounting, all future costs and benefits were summed and discounted as if they occurred just 1 year into the future. This has the impact of over-estimating the net present value of QALYs relative to costs.

The model itself is an extrapolation of 1-year VA gain linked to utility and extrapolated over a further 30 year period. It is not clear whether BSE or WSE utility is used and utility decrements for pain, photophobia and burning have no referenced source. There is no sensitivity analysis regarding the assumption of time-invariant effectiveness over the 30-year period despite the evidence source duration being just 1 year.

## *5.2 De novo analysis*

The unilateral model and bilateral model discussed below are presented in Appendix 5 and Appendix 6 respectively.

*Patient population*

The patient population consists of adults with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1 - 2 $mm^2$ of undamaged limbus.(6)

Patients of the HLSTM01 trial(7) are taken as being representative of the potential patient population and reflect a mixture of incident patients who have fairly recently suffered injury and a prevalent population who may have waited decades for an effective treatment. Incidence of ocular symptoms such as pain, burning and photophobia are taken from the trial data. In addition the incidence of underlying stromal scarring which may be corrected (via keratoplasty) if and only if a stable ocular surface is restored is also taken from the trial data.

*Model structure*

To capture the treatment pathways and natural history a de novo model was developed. The model for the unilateral HOLOCLAR arm is described in detail

below. The models for the other active comparators follow the same structure. For best supportive care a simple 2 state Markov model was developed.

The model can be split into 2 constituent parts: i) a decision tree capturing the acute treatment pathways, and ii) a Markov model capturing the longer term outcomes of the patient. These are described in turn below.

Figure 14 presents the acute treatment pathway for patients with unilateral LSCD undergoing HOLOCLAR. Patients initially undergo a biopsy procedure, if this biopsy is successful they progress to implantation with HOLOCLAR. If the initial biopsy procedure is unsuccessful they undergo a second biopsy procedure, if this is successful they progress to HOLOCLAR implantation, if it is unsuccessful, they are classed as a failure and enter the Markov model in the Failure state. Following a successful biopsy, the patient undergoes HOLOCLAR implantation. If the implantation is successful, they enter the Stable Month 1 to 12 state in the Markov model. If the implantation is unsuccessful they enter the Failure state. Each biopsy involves an associated cost and health related quality of life decrement.

**Figure 14: Decision tree for HOLOCLAR – Unilateral LSCD**

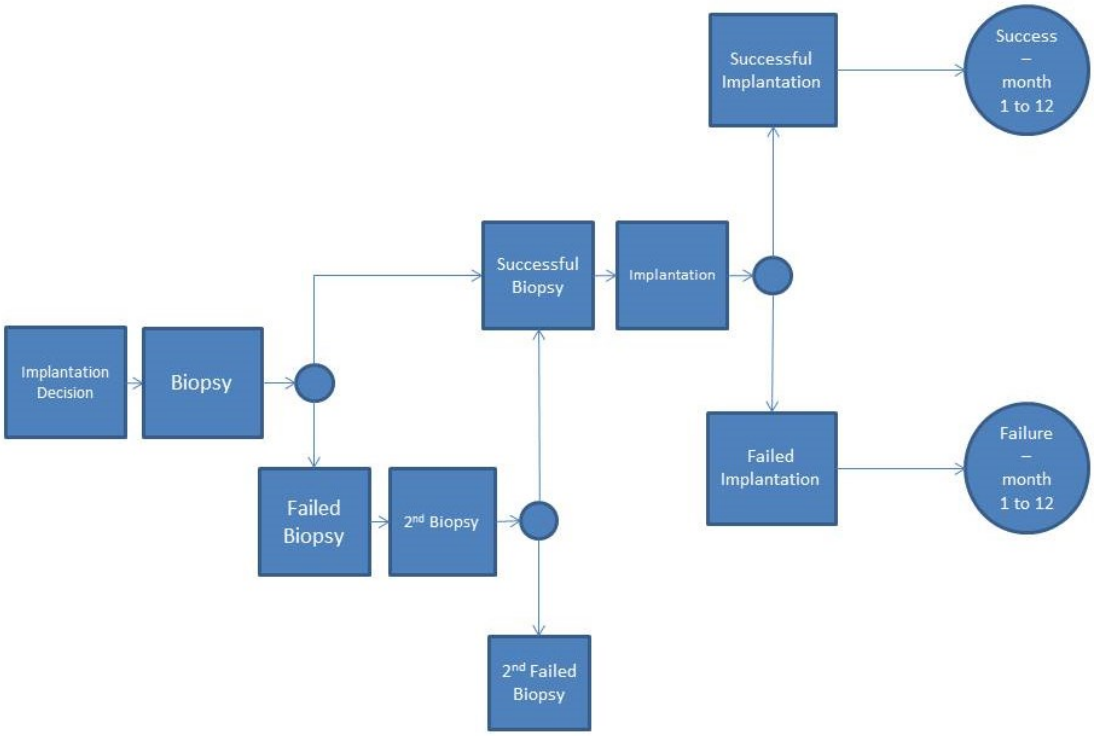
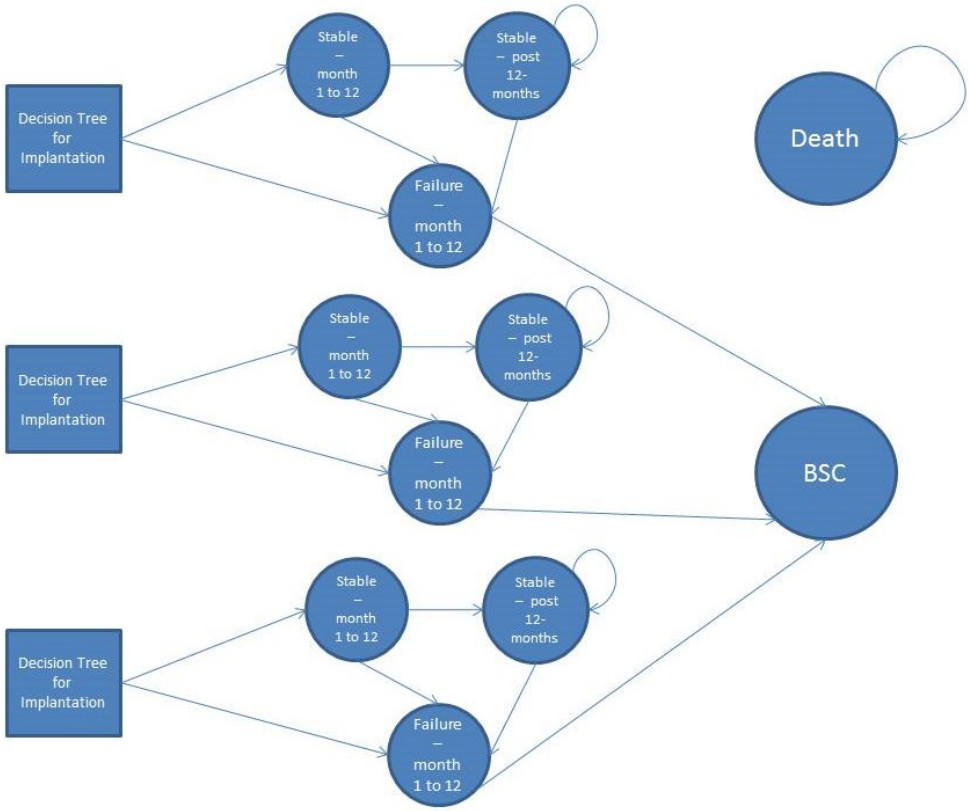


Figure 15 presents the Markov model for the long-term extrapolation of patients with HOLOCLAR. The model has a 1 year time cycle. Following the acute treatment stage captured by the decision tree described above, patients enter the Markov model in either the Operation 1 Stable Months 1 to 12 state or the Operation 1 Failure state. Those in the stable state can either remain stable and progress to the Operation 1 Stable post 12 months state or they can fail and move to the failure state. For those who remain stable and progress to the post 12 months state, some will be eligible for a keratoplasty at 12 months. The costs and impact of this on visual acuity are captured at the point of transition and in the ongoing health related quality of life associated with the stable state. Patients who enter the Post 12 month state will continue in this state or at some point in the future their HOLOCLAR will fail and they will move to the Op 1 HOLOCLAR failure state.

Patients in the failure state will remain there for 1 year, at which point they will either undergo a second acute HOLOCLAR treatment pathway (captured by re-entering the decision tree) or they will be transferred to best support care. Following a second HOLOCLAR acute treatment pathway, the possible states are the same as for the initial pathway. Patients can undergo a maximum of 3 acute treatment pathways. From all states in the model patients can die, with mortality estimated from UK life tables.

Each state in the model has associated costs and health related quality of life.

**Figure 15: Markov model for HOLOCLAR – Unilateral LSCD**




The same model structure has been used for all of the active comparators to HOLOCLAR for unilateral disease. For CLAU it is assumed there is no separate biopsy procedure.

For best supportive care a simple two state Markov model has been developed with states for alive and dead and cost and health related quality of life associated with the alive state.

*Bilateral model*

For the bilateral model, the same structure as the unilateral model has been used for each eye. It is expected that only one eye would be treated at a time and that there would be a delay between treatments of one year. Therefore, for the second eye treated, an additional first year without treatment state has been included. At the end of this year, patients enter the treatment decision tree for that eye. To capture the quality of life of patients with bilateral disease, the average health related quality of life across both eyes is taken.

**Table 20: Features of the de novo analysis**

| Factor | Chosen values | Justification |
|---|---|---|
| Time horizon | Life-time | As per reference case model |
| Were health effects measured in QALYs; if not, what was used? | QALYs | As per reference case model |
| Discount of 3.5% for utilities and costs | 1.5% | Long term effectiveness combined with return to high utility state |
| Perspective (NHS/PSS) | NHS/PSS perspective | As per reference case model |
| PSS, personal social services; QALYs, quality-adjusted life years | | |

*Intervention technology and comparators*

The intervention being considered is HOLOCLAR, an ex vivo expanded autologous human corneal epithelial cell transplant containing stem cells.

For people with moderate to severe unilateral and bilateral limbal stem cell deficiency due to physical or chemical ocular burns, the alternative modelled treatments are:

- Conjunctival-limbal autograft (CLAU)
- limbal epithelial stem cells allografts : living-related conjunctival allograft (lr-CLAL)
- limbal epithelial stem cells allografts : keratolimbal allogeneic transplantation (KLAL)
- best supportive care (BSC)

## *5.3 Clinical parameters and variables*

The key clinical parameters are: the condition of the cornea i.e. presence of a stable cornea with little or no defects or blood vessels present in the cornea and the presence or absence of stromal scarring; the relationship between these parameters and VA and the relationship with other ocular symptoms pain/burning/photophobia and disfigurement.

A successful transplant is regarded as one which restores a stable cornea with little or no defects or blood vessels present in the cornea. The probabilities of each of the comparator interventions achieving a successful (and maintaining) stable ocular surface are determined from the literature. The impact of achieving a stable surface is derived from the following analyses. This section therefore details a bespoke analysis of the HLSTM01(7) data which, given the single-arm nature of the observational data, yields a relationship between HOLOCLAR transplant success and the clinical variables which may influence HRQoL. However, in the absence of corresponding relevant data for comparators being identified in the literature review, some of the parameters we estimate will be used to populate the comparator arms of the economic model. For example, the relationship between a successful transplant and VA measured here with HOLOCLAR will be assumed to hold for the transplant successes of other alternative treatments provided there has not been a transplant failure rejection over time. So for example, although there is a tendency for Ir-CLAL and KLAL to fail over time (and measured in the literature), until the point at which they actually fail the benefit in terms of impact on VA is the same as that of HOLOCLAR. We believe that this is a conservative assumption from the perspective of HOLOCLAR.

As described in 4.11.5 HLSTM01 is a single-arm observational study of 113 eyes followed over a maximum period of 10 years.(7) Out of the 113 eyes, 103 are recorded as having LSCD as being secondary to chemical or thermal burns and these data are used in the analysis. As a sensitivity analysis all analyses were repeated using the full data sample and all results were robust to the choice of underlying data.

Complete examination of the eye took place at baseline, one year post-surgery and then every year up to a maximum of 10 years and thus a maximum of 11 observations per eye. The median length of follow-up was 3 years with an inter-quartile range of 2 to 4 years. 16 eyes had just one-year follow-up and one eye had the full 10 year worth of follow-up observations.

In each examination VA of the eye was measured with captured responses ranging from light perception (LP), hand movement (HM), finger count (FC) to continuous measures of natural visus (/10) and BCVA (/10). For the purposes of the analysis the

highest visual acuity response was used, this was primarily a small number of cases where both natural and BCVA were measured.

The presence and extent of pain burning and photophobia were also captured at each eye examination via separate ordered categorical response variables (responses: none/mild/moderate/severe).

Stromal scarring was measured by a corneal opacity variable initially capturing a dichotomous presence yes or no and then in the presence of opacity whether this was superficial or deep. In principle this permits an ordered category no opacity/superficial/deep but in practice a number of responses checked both superficial and deep scarring. This created a fourth category of 'superficial or deep'. In line with the existing analysis of the HLSTM01 data a stromal scarring variable is created with its absence or presence indicated respectively with no opacity or superficial opacity responses and superficial and deep or deep opacity.

The success of the transplantation was recorded at one-year follow-up and was based on the following responses: Superficial corneal neo-vascularization = 'None (No vessel penetration)' or 'Mild (vessel penetration 1 quadrant (up to 3 hours o'clock) without central cornea involved) and Epithelial defects by fluorescein staining = 'None (No staining) or 'Minimal superficial staining, pooling'.

Table 21 shows the distribution of VA in the affected eye at baseline as well as the mean duration of LSCD prior to treatment and follow-up for each presenting baseline VA.

**Table 21: VA at baseline, duration of LSCD and follow-up duration**

| Baseline VA | Frequency | Duration of LSCD prior to transplant (years) | Mean Follow-Up Duration (Months) |
|---|---|---|---|
| Missing | 1 | 4 | 24 |
| LP | 10 | 15.7 | 49 |
| HM | 38 | 19.3 | 45 |
| FC | 38 | 20.2 | 35 |
| 0.05 | 1 | 5 | 24 |

| | | | |
|---|---|---|---|
| 0.1 | 2 | 5.5 | 18 |
| 0.2 | 7 | 16.9 | 29 |
| 0.3 | 1 | 57 | 48 |
| 0.4 | 1 | 53 | 96 |
| 0.5 | 1 | 7 | 12 |
| 0.6 | 1 | 7 | 12 |
| 0.7 | 2 | 19.5 | 48 |

The table shows a number of important characteristics. Firstly that patients in the trial present with very low VA. This is an issue for attaching HRQoL values as such VA states are often outside the range measured in observational studies. The second element is that although there is substantial variation in follow-up between patients there is no systematic tendency to follow patients with better VA longer than patients with lower VA. Indeed the longest follow-up period is of a patient with a visual acuity of FC in the WSE.

This has important consequences for considering the robustness of the results that follow. We return to this issue with a more formal analysis, but the conclusion remains as illustrated in the simple table – it is the eyes with the lower VA at baseline which have persistently longer follow-up, it is therefore unlikely that results over time are biased by a non-random selection of better seeing eyes driving results. The third pertinent feature is the duration of LSCD prior to treatment with HOLOCLAR, with some patients having suffered for many decades. This indicates a lack of effective alternative treatment but also there may need to be a distinction made between an incidence and prevalent population. The average age of HLSTM01 patient population is 46 years whereas the average of the population at injury is 28 years.(7)

### 5.3.1 The relationship between transplantation success, stromal scarring and VA

To estimate the relationship between VA and successful transplantation a random effects ordered logistic regression model was estimated using the GLIMMIX procedure in SAS 9.3. VA was converted to a 13 point ordered scale ranging from Light Perception to 10/10 BCVA. To account for underlying patient heterogeneity and the clustering of results within patients, random effects for all individual patients were

estimated. An alternative model using fixed effects was also estimated and produced similar results with identical substantive conclusions. The random effects specification is preferred on the basis of theoretical grounds, with the posterior distribution of the estimated random effects reflecting the distribution of heterogeneity in a future patient population.

A base case model with Explanatory variables *transplantation status* (Baseline / successful [omitted category in regression]/ failure) and a dummy variable for presence of *stromal scarring* is initially estimated. The underlying motivation for the model is that each eye has its own underlying VA, which may vary across eyes, and is affected by transplant success or failure and the presence or absence of stromal scarring.

A simplifying assumption of this model is that it assumes that the relationship between transplant success (measured at one time, 12 months after transplant) and VA (conditional on the presence/absence of stromal scarring) is constant over time. If it is plausible that HOLOCLAR transplant fails or becomes less effective over time then the regression model may be inappropriate to be used in a model which extrapolates the results over a time period which is considerably longer than the trial duration. Therefore an alternative model is estimated which adds to the base case model a dynamic element by introducing a month variable and a successful transplant dummy multiplied by month to give a successful transplant and time interaction. If the effect of a successful HOLOCLAR transplant declines over time then we would expect a statistically significant negative coefficient attached to the successful transplant * time interaction.

The adoption of a random effects specification not only accounts for the clustering of observations within patients, but also provides a means of addressing the issue of differing lengths of follow-up which are mainly a function of differing recruitment times on to the trial. The time-varying model may be biased if there are systematic differences between individuals that provide longer follow-up than those that do not. For example the individual who provides 10 year worth of data reports a VA of FC in the final observation. This is the only observation at 10 years and thus an influential data point. A failure to explicitly account for a potential difference in this patient's underlying status may bias the results – is the low VA a function of a declining VA of

an average individual over time or a sustained VA of a below average individual? Inspection of this particular individual's results over time shows that they reported a VA of LP at baseline, they had a successful HOLOCLAR transplant but unresolved stromal scarring at all further time points. At each annual follow-up point the patient consistently reported a VA of FC with absolutely no variation. In this particular case we clearly have an individual with a below-average VA consistently reporting an improved but still fairly low VA over time – there is no decline in VA over time. The random effects model allows us a statistical technique to distinguish between these potential situations.

**Table 22: Random effects models of the relationship between transplantation success and VA over time**

| Effect | Level | Time Invariant Model | | Time Varying Model | |
|---|---|---|---|---|---|
| | | Estimate | Std Error | Estimate | Std Error |
| **VA Threshold** | HM | -8.6406 | 0.5336 | -8.4207 | 0.5752 |
| **VA Threshold** | FC | -5.5845 | 0.4032 | -5.3335 | 0.4552 |
| **VA Threshold** | 1 | -2.5933 | 0.3315 | -2.2895 | 0.3951 |
| **VA Threshold** | 2 | -1.8262 | 0.3202 | -1.5247 | 0.3868 |
| **VA Threshold** | 3 | -1.0483 | 0.3114 | -0.7478 | 0.3806 |
| **VA Threshold** | 4 | -0.403 | 0.3072 | -0.1041 | 0.3779 |
| **VA Threshold** | 5 | 0.5144 | 0.3088 | 0.8063 | 0.3799 |
| **VA Threshold** | 6 | 1.2197 | 0.3189 | 1.5068 | 0.3891 |
| **VA Threshold** | 7 | 1.8621 | 0.3371 | 2.1467 | 0.4056 |
| **VA Threshold** | 8 | 2.5635 | 0.3702 | 2.8487 | 0.4352 |
| **VA Threshold** | 9 | 4.2819 | 0.5476 | 4.5845 | 0.5975 |
| **VA Threshold** | 10 | 5.8207 | 0.8945 | 6.1338 | 0.9278 |
| **Stromal Scaring** | Present | -2.7374 | 0.2833 | -2.6359 | 0.2879 |
| **Baseline** | Baseline | -2.8865 | 0.2956 | -2.7195 | 0.339 |
| **Transplant Outcome** | Fail | -1.5104 | 0.4366 | -1.5788 | 0.6344 |
| **Transplant Outcome** | Success | 0 | . | 0 | . |
| **Month** | | | | 0.01164 | 0.01766 |
| **Transplant Success * Month** | | | | -0.003921 | 0.01873 |
| | | | | | |
| **Eye-Level Random Effect** | Std Dev | 4.2449 | 0.863 | 4.3933 | 0.888 |
| | | | | | |
| **-2 Res Log Pseudo-Likelihood** | | 24297.85 | | 24396.19 | |
| **Pseudo-AIC** | | 24299.85 | | 24398.19 | |
| **Pseudo-BIC** | | 24302.49 | | 24400.82 | |

There are 415 potential observations in the dataset. 411 are used in the regression model. 4 observations are excluded on the basis of missing VA data. The missing data are considered MAR and are thus ignorable. Both models successfully converged.

The regression models have similar results in terms of estimates, standard errors, distribution of random effects and goodness of fit. We note that neither of the time variables in the time-varying model are close to statistical significance and the AIC and BIC penalised-likelihood goodness of fit models suggest a better for the time-invariant model. This is compelling evidence that the impact of a successful HOLOCLAR transplant is consistent over time and we use the time-invariant model to populate our economic model from this point forward.

In terms of substantive results it is clear that a successful transplant increases the probability of improved VA, both in terms of statistical and practical significance. It is also noted that the impact of stromal scarring is of a similar important practical and statistical magnitude. This has two main implications for both modelling and also evidence synthesis. Firstly in terms of modelling, removal of stromal scarring via a keratoplasty is possible only in the event of successful limbal stem cell transplantation and this needs to be reflected in the model.

In terms of evidence synthesis, it makes it difficult to compare studies which use VA as the measure of interest when it is not clear how many or which patients have also undertaken keratoplasties. There may also be issues with early evidence where keratoplasty was often conducted at the same time as the transplant graft. It has since been noted in the literature that a two-step practice in conducting keratoplasty only after a successful transplant and inflammation has died down (6 months plus) is more likely to lead to sustained success. Thus early studies using VA as outcome measures may be unduly influenced by a high rate of failed keratoplasties.

Of further note in the regression results is the measured impact of a failed transplant, which yields a statistically significant coefficient to that of baseline. This implies that there is some improvement in VA even if the transplant is regarded as a failure. This may be a function of the definition of what is categorised as a successful transplantation or not. For example there are several eyes in the data which move

from a severe to moderate neovascularisation of the cornea (and are thus regarded as failures) and as a result yield some expected improvement in VA.

The final issue of note in the regression results is the eye-level heterogeneity captured by the random effects. The model estimates a distribution ranging from 5.26 to -6.15 and 25th percentile and 75th percentile thresholds of 1.07 and -1.12 respectively - a wide range reflecting large differences in underlying VA with or without a stable ocular surface and the presence or absence of stromal scarring. High positive values represent good underlying VA and negative values indicate poor underlying VA. Thus even successful transplantation and removal of stromal scarring may not restore good VA to some patients. For example the random effect estimated for our eye which provided 10 year worth of follow-up data was -1.51 indicating that individual is in the lowest 25th percentile of underlying VA.

Although inspection of the raw regression results is in itself informative, it is more useful to look at the impact of eye characteristic on the probability of achieving the ordered VA categories. Table 23 shows the expected probabilities, cumulative and individual, for each VA state for all combinations of characteristics (from baseline with stromal scarring to successful transplant without stromal scarring) for an average affected eye (i.e. random effect = 0). Probabilities are calculated via the following equation.

$$\Pr(VA = y) = \frac{e^{\kappa_y - x'\beta}}{1 + e^{\kappa_y - x'\beta}} - \frac{e^{\kappa_{(y-1)} - x'\beta}}{1 + e^{\kappa_{(y-1)} - x'\beta}}$$

The probability of a VA state y being reported is the difference between the cumulative probability of y or lower being reported minus the cumulative probability of the state below y (i.e. y-1) or below being reported. κ_y represents the estimated threshold between state y and state y-1.

Table 23 shows the calculated probabilities of each VA state for an average eye given combinations of explanatory variables indicating whether it is baseline, whether it is post-successful or post-failure transplantation and whether stromal scarring is present or absent.

For example the probability of an average patient with stromal scarring has a 95.39% probability of reporting a VA of FC or less at baseline, with a 46.32% of specifically

reporting HM and 44.41% of reporting FC. That same patient at the same time point but without stromal scaring has a 57.28% probability of reporting a VA of FC or less at baseline, and a 5.99% of reporting HM and a 50.97% of reporting FC. If the same patient is able to have a successful HOLOCLAR transplant and then a successful keratoplasty removing stromal scarring then they have just a 6.96% probability of reporting a VA of FC or less, a 0.36% of reporting HM and a 6.58% chance of reporting FC. For such a patient the most likely reported VA state is 4/10 with a probability of 22.52%

The impact of a failed transplantation may also be estimated. For our average baseline patient with stromal scarring there is also a positive impact of a failed transplant – reading from Table 23 it can be seen that they would have an 83.95% probability of reporting a VA of FC or less, a 19.58% of reporting HM and a 63.14% chance of reporting FC.

As the model is non-linear then the expectation of the average eye is not the average of the expectations across the population of heterogeneous eyes. And as the estimation revealed a wide distribution of underlying VA then for modelling purposes it is thus important to accommodate the expectations of eyes which naturally have better and worse underlying VA.

For example, for our eye with 10 year worth of follow-up data and a consistently reported VA of FC after successful transplant but remaining stromal scarring, we can plug the estimated RE of -1.51 into the prediction equation and see that the model predicted that they were indeed most likely to report a post-baseline VA of FC with a 63.13% probability and only a 15.99% probability of achieving a VA above FC. If we were able to resolve this individual's stromal scarring then the model still predicts a most likely VA of just FC, but this time with a lower probability of 23.7% and a 74.62% probability of reporting a higher VA than FC.

To accommodate the likely heterogeneity that patients may be likely to present with and give the decision maker an idea of the average of expectations across a heterogeneous population rather than simply the expectation of the average we define three types of eyes based on underlying VA – average, good and poor. We attach values to these representative eyes by defining poor [good] as being in the

bottom [top] 25% of the estimated random effects and assigning the relevant portioned distribution mean values to these categories. We thus estimate an eye with poor / average / good underlying VA to have individual specific intercepts of - 2.30 / 0 / 2.30 respectively. Table 24 and Table 25 show the equivalent probabilities of reporting the ordered VA states for patients with 2.30 and -2.30 specific intercepts and whether they have successful transplants, etc.

For example for a patient with good underlying VA and with stromal scarring at baseline has a 58.05% probability of reporting FC and with a successful transplant and removal of stromal scarring is most likely to report a 8/10 BCVA with a probability of 31.34% For an eye with poor underlying VA with stromal scarring the most likely reported VA at baseline is HM at 58.4% but even after a successful transplant and subsequent removal of stromal scarring, the most likely reported state is FC at 39.11%.

An important feature of the results is that it is not always possible to determine the underlying potential to improve VA from presenting VA alone. Naturally if patients present with a current BCVA of 0.7 then there is a strong signal that the underlying VA is good. However if a patient presents with a BCVA of HM then it is not possible to accurately predict whether they have good, bad or average underlying VA especially when it is not possible to determine the presence or absence of stromal scarring.

As a further check of within sample goodness of fit we can calculate the implied probabilities of VA states for all observations by applying the estimated coefficients from the regression model to the actual characteristics of all observations used in the regression model, including eye-specific random effects (i.e. best linear unbiased predictions [BLUP]). We may sum these probabilities and compare against actual observed categories as a means of measuring the within-sample goodness of fit. In order to apply one further measure of goodness of fit over time, we compare observed (Obs) with predicted (Pred) for each of the scheduled annual visits. These results are shown in Table 26.

As can be seen the model produces estimates which closely match the observed VA states. Importantly there is no evidence of systematic deviances or changes in

predictive power between Obs and Pred over time. The comparison of observed and expected outcomes over time and the close relationship therefore provides further prima facia evidence of a good fit between model and data. As such it should also be noted that observed decline in higher rates of VA being reported over time is not a function of a group of patients with declining VA over time but a longer follow-up of patients who have naturally lower underlying VA which may well be a reflection of patient selection in the earlier years.

For modelling purpose we will assume that the estimated relationship between successful HOLOCLAR treatment and VA is the same as the relationship between any successful transplant and VA. The model does permit differing rates of failure over time between different treatment options (specifically between the allografts and autologous grafts) but if a transplant is still successful then we assume the impact is the same, we believe that this is plausible and conservative assumption.

**Table 23: Probability of VA states for the average affected eye**

| | Baseline with SS | | Baseline w/o SS | | Transplant Failure with SS | | Transplant Failure w/o SS | | Transplant Success with SS | | Transplant Success w/o SS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XB | -5.6239 | | -2.8865 | | -4.2478 | | -1.5104 | | -2.7374 | | 0 | |
| Visual Acuity (ordered cat level) | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** |
| LP (1) | 4.67% | **4.67%** | 0.32% | **0.32%** | 1.22% | **1.22%** | 0.08% | **0.08%** | 0.27% | **0.27%** | 0.02% | **0.02%** |
| HM (2) | 50.98% | **46.32%** | 6.31% | **5.99%** | 20.81% | **19.58%** | 1.67% | **1.59%** | 5.48% | **5.21%** | 0.37% | **0.36%** |
| FC (3) | 95.39% | **44.41%** | 57.28% | **50.97%** | 83.95% | **63.14%** | 25.30% | **23.62%** | 53.60% | **48.11%** | 6.96% | **6.58%** |
| 1 (4) | 97.81% | **2.41%** | 74.27% | **17.00%** | 91.85% | **7.90%** | 42.17% | **16.87%** | 71.32% | **17.73%** | 13.87% | **6.91%** |
| 2 (5) | 98.98% | **1.17%** | 86.27% | **12.00%** | 96.08% | **4.24%** | 61.35% | **19.18%** | 84.41% | **13.09%** | 25.96% | **12.09%** |
| 3 (6) | 99.46% | **0.48%** | 92.30% | **6.02%** | 97.91% | **1.82%** | 75.16% | **13.81%** | 91.17% | **6.76%** | 40.06% | **14.10%** |
| 4 (7) | 99.78% | **0.32%** | 96.77% | **4.48%** | 99.15% | **1.25%** | 88.34% | **13.17%** | 96.27% | **5.11%** | 62.58% | **22.52%** |
| 5 (8) | 99.89% | **0.11%** | 98.38% | **1.61%** | 99.58% | **0.43%** | 93.88% | **5.54%** | 98.12% | **1.85%** | 77.20% | **14.62%** |
| 6 (9) | 99.94% | **0.05%** | 99.14% | **0.76%** | 99.78% | **0.20%** | 96.68% | **2.81%** | 99.00% | **0.88%** | 86.55% | **9.35%** |
| 7 (10) | 99.97% | **0.03%** | 99.57% | **0.43%** | 99.89% | **0.11%** | 98.33% | **1.64%** | 99.50% | **0.50%** | 92.85% | **6.29%** |
| 8 (11) | 100.00% | **0.02%** | 99.92% | **0.35%** | 99.98% | **0.09%** | 99.70% | **1.37%** | 99.91% | **0.41%** | 98.64% | **5.79%** |
| 9 (12) | 100.00% | **0.00%** | 99.98% | **0.06%** | 100.00% | **0.02%** | 99.93% | **0.24%** | 99.98% | **0.07%** | 99.70% | **1.07%** |
| 10 (13) | 100.00% | **0.00%** | 100.00% | **0.02%** | 100.00% | **0.00%** | 100.00% | **0.07%** | 100.00% | **0.02%** | 100.00% | **0.30%** |

**Table 24: Probability of VA states for eye with 'good' underlying VA (Random Effect = 2.3)**

| | Baseline with SS | | Baseline w/o SS | | Transplant Failure with SS | | Transplant Failure w/o SS | | Transplant Success with SS | | Transplant Success w/o SS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XB | -3.3239 | | -0.5865 | | -1.9478 | | 0.7896 | | -0.4374 | | 2.3 | |
| Visual Acuity | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** |
| LP | 0.49% | **0.49%** | 0.03% | **0.03%** | 0.12% | **0.12%** | 0.01% | **0.01%** | 0.03% | **0.03%** | 0.00% | **0.00%** |
| HM | 9.44% | **8.96%** | 0.67% | **0.64%** | 2.57% | **2.44%** | 0.17% | **0.16%** | 0.58% | **0.55%** | 0.04% | **0.04%** |
| FC | 67.49% | **58.05%** | 11.85% | **11.18%** | 34.40% | **31.83%** | 3.28% | **3.11%** | 10.38% | **9.80%** | 0.74% | **0.71%** |
| 1 | 81.72% | **14.23%** | 22.45% | **10.60%** | 53.04% | **18.64%** | 6.81% | **3.53%** | 19.96% | **9.58%** | 1.59% | **0.84%** |
| 2 | 90.68% | **8.96%** | 38.66% | **16.21%** | 71.08% | **18.05%** | 13.73% | **6.92%** | 35.19% | **15.23%** | 3.40% | **1.81%** |
| 3 | 94.89% | **4.20%** | 54.57% | **15.92%** | 82.42% | **11.33%** | 23.28% | **9.55%** | 50.86% | **15.67%** | 6.28% | **2.88%** |
| 4 | 97.89% | **3.01%** | 75.04% | **20.47%** | 92.14% | **9.73%** | 43.16% | **19.88%** | 72.15% | **21.29%** | 14.36% | **8.08%** |
| 5 | 98.95% | **1.06%** | 85.89% | **10.85%** | 95.96% | **3.81%** | 60.59% | **17.43%** | 83.98% | **11.84%** | 25.34% | **10.98%** |
| 6 | 99.44% | **0.50%** | 92.05% | **6.16%** | 97.83% | **1.87%** | 74.51% | **13.92%** | 90.88% | **6.90%** | 39.22% | **13.88%** |
| 7 | 99.72% | **0.28%** | 95.89% | **3.84%** | 98.91% | **1.08%** | 85.49% | **10.99%** | 95.26% | **4.38%** | 56.55% | **17.33%** |
| 8 | 99.95% | **0.23%** | 99.24% | **3.35%** | 99.80% | **0.89%** | 97.05% | **11.55%** | 99.12% | **3.85%** | 87.89% | **31.34%** |
| 9 | 99.99% | **0.04%** | 99.84% | **0.60%** | 99.96% | **0.15%** | 99.35% | **2.30%** | 99.81% | **0.69%** | 97.13% | **9.24%** |
| 10 | 100.00% | **0.01%** | 100.00% | **0.16%** | 100.00% | **0.04%** | 100.00% | **0.65%** | 100.00% | **0.19%** | 100.00% | **2.87%** |

**Table 25: Probability of VA states for eye with 'poor' underlying VA (Random Effect = -2.3)**

| | Baseline with SS | | Baseline w/o SS | | Transplant Failure with SS | | Transplant Failure w/o SS | | Transplant Success with SS | | Transplant Success w/o SS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XB | -7.9239 | | -5.1865 | | -6.5478 | | -3.8104 | | -5.0374 | | -2.3 | |
| Visual Acuity | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** |
| LP | 32.81% | **32.81%** | 3.06% | **3.06%** | 10.98% | **10.98%** | 0.79% | **0.79%** | 2.65% | **2.65%** | 0.18% | **0.18%** |
| HM | 91.21% | **58.40%** | 40.18% | **37.11%** | 72.38% | **61.40%** | 14.50% | **13.71%** | 36.65% | **34.00%** | 3.61% | **3.43%** |
| FC | 99.52% | **8.31%** | 93.04% | **52.86%** | 98.12% | **25.74%** | 77.16% | **62.65%** | 92.01% | **55.36%** | 42.72% | **39.11%** |
| 1 | 99.78% | **0.26%** | 96.64% | **3.60%** | 99.12% | **1.00%** | 87.91% | **10.76%** | 96.13% | **4.11%** | 61.63% | **18.91%** |
| 2 | 99.90% | **0.12%** | 98.43% | **1.79%** | 99.59% | **0.48%** | 94.06% | **6.15%** | 98.18% | **2.06%** | 77.76% | **16.13%** |
| 3 | 99.95% | **0.05%** | 99.17% | **0.74%** | 99.79% | **0.19%** | 96.79% | **2.73%** | 99.04% | **0.86%** | 86.96% | **9.20%** |
| 4 | 99.98% | **0.03%** | 99.67% | **0.50%** | 99.91% | **0.13%** | 98.69% | **1.90%** | 99.61% | **0.58%** | 94.34% | **7.39%** |
| 5 | 99.99% | **0.01%** | 99.84% | **0.17%** | 99.96% | **0.04%** | 99.35% | **0.66%** | 99.81% | **0.20%** | 97.12% | **2.78%** |
| 6 | 99.99% | **0.01%** | 99.91% | **0.08%** | 99.98% | **0.02%** | 99.66% | **0.31%** | 99.90% | **0.09%** | 98.47% | **1.34%** |
| 7 | 100.00% | **0.00%** | 99.96% | **0.04%** | 99.99% | **0.01%** | 99.83% | **0.17%** | 99.95% | **0.05%** | 99.23% | **0.77%** |
| 8 | 100.00% | **0.00%** | 99.99% | **0.04%** | 100.00% | **0.01%** | 99.97% | **0.14%** | 99.99% | **0.04%** | 99.86% | **0.63%** |
| 9 | 100.00% | **0.00%** | 100.00% | **0.01%** | 100.00% | **0.00%** | 99.99% | **0.02%** | 100.00% | **0.01%** | 99.97% | **0.11%** |
| 10 | 100.00% | **0.00%** | 100.00% | **0.00%** | 100.00% | **0.00%** | 100.00% | **0.01%** | 100.00% | **0.00%** | 100.00% | **0.03%** |

**Table 26: Comparison of observed and BLUP predictions of VA over time**

| VA | Baseline | | Year 1 | | Year 2 | | Year 3 | | Year 4 | | Year 5 | | Year 6 | | Year 7 | | Year 8 | | Year 9 | | Year 10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred | Obs | Pred |
| **LP** | 10 | 10 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **HM** | 38 | 37 | 17 | 12 | 5 | 6 | 6 | 5 | 2 | 4 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **FC** | 38 | 39 | 41 | 37 | 19 | 22 | 11 | 14 | 13 | 11 | 6 | 6 | 4 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |
| **1** | 3 | 5 | 11 | 11 | 7 | 8 | 4 | 5 | 2 | 3 | 3 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| **2** | 7 | 4 | 11 | 10 | 7 | 8 | 4 | 5 | 3 | 3 | 1 | 2 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| **3** | 1 | 2 | 2 | 7 | 8 | 6 | 4 | 4 | 3 | 3 | 2 | 1 | 1 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 |
| **4** | 1 | 2 | 9 | 8 | 5 | 8 | 5 | 5 | 4 | 4 | 4 | 2 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **5** | 1 | 1 | 5 | 5 | 7 | 5 | 3 | 4 | 3 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **6** | 1 | 1 | 1 | 3 | 8 | 4 | 4 | 3 | 0 | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **7** | 2 | 1 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **8** | 0 | 1 | 1 | 3 | 4 | 3 | 5 | 3 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| **9** | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **10** | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### 5.3.2 The relationship between pain/burning/photophobia and successful transplantation and stromal scarring

Pain, burning and photophobia are all elements which may be reasonably expected to yield a utility decrement where present. Data are separately collected in all 3 elements during all eye examinations. As previously described they are collected via self-reported responses on an ordered scale (none / mild / moderate / severe).

Table 27 shows the distribution at baseline and Table 28 the distribution across all data points of the 103 eyes that reported meeting the thermal or chemical burn criteria. An additional 'any' category has been created by recording the maximum level of severity across any of the three individual elements.

**Table 27: Baseline**

| | None | Mild | Moderate | Severe | Missing |
|---|---|---|---|---|---|
| Pain | 96 | 4 | 0 | 0 | 3 |
| Burning | 73 | 18 | 9 | 0 | 3 |
| Photophobia | 68 | 17 | 14 | 1 | 3 |
| Any | 63 | 19 | 17 | 1 | 3 |

**Table 28: All observations**

| | None | Mild | Moderate | Severe | Missing |
|---|---|---|---|---|---|
| Pain | 385 | 5 | 1 | 0 | 24 |
| Burning | 342 | 37 | 11 | 0 | 25 |
| Photophobia | 331 | 36 | 18 | 1 | 29 |
| Any | 321 | 48 | 22 | 1 | 23* |

* The combined category was created using the maximum valid result from any of the three separate variables hence the number of missing observations is lower than the number of missing values from the individual categories.

The data show that 63% of eyes reported no additional symptoms at baseline and 77% no additional symptoms in the overall set of 415 observations. We note that there were especially few patients that reported pain. Rama argues that the low prevalence of these elements in the trial population is a function of the length of time

following the initial injury and that they would be higher in an incidence population. We also note the high degree of correlation between symptoms which is demonstrated by the total volumes in the any category closely matching those in photophobia and burning especially at baseline. As such we use the combined category to understand the relationship between these symptoms, transplant success and stromal scarring.

As with VA we estimate a random effects ordered logit model with the combined symptoms outcome as the dependent variable and stromal scarring and transplant outcome (baseline, success [omitted category] and failure) as explanatory variables. Results are shown in Table 29.

**Table29: Regression model of impact of transplant on pain/burning /photophobia**

| Effect | Level | Estimate | Standard Error | t Value |
|---|---|---|---|---|
| **Pain/Burning/Photophobia Threshold** | None to Mild | 3.09 | 0.40 | 7.82 |
| **Pain/Burning/Photophobia Threshold** | Mild to Moderate | 4.60 | 0.45 | 10.29 |
| **Pain/Burning/Photophobia Threshold** | Moderate to Severe | 7.97 | 1.13 | 7.04 |
| **Stromal Scaring** | Present | 1.04 | 0.42 | 2.5 |
| **Baseline** | Baseline | 1.75 | 0.33 | 5.36 |
| **Transplant Outcome** | Fail | 0.81 | 0.46 | 1.74 |
| **Transplant Outcome** | Success | 0 | . | . |
| | | | | |
| **Eye-Level Random Effect** | Std Dev | 0.726 | 0.3581 | |
| | | | | |
| **-2 Res Log Pseudo-Likelihood** | | 6056.57 | | |
| **Pseudo-AIC** | | 6058.57 | | |
| **Pseudo-BIC** | | 6061.21 | | |

Positive values indicate a tendency to report higher levels of symptoms. The results are qualitatively similar to the VA regression results in that the presence of stromal scarring, pre-operative status and failed transplant are all more likely to lead to

worse outcomes than the absence of stromal scarring and a successful transplant. Unlike the VA regression there is no statistical significance between a failed and successful transplant. The eye-level measure of heterogeneity is just about significant indicating that different eyes have different probabilities of generating reports of pain, burning or photophobia, but that the degree of heterogeneity is smaller than that which drives VA.

Table 30 shows the probabilities of reporting levels of symptoms for the average patient under differing conditions. An eye with stromal scarring at baseline has a 57.47% probability of reporting no symptoms and this increases to 95.65% following a successful transplant and then subsequent removal of stromal scarring.

Inspection of the estimated eye-level random effects indicates that the overwhelming majority of individual effects are not significantly different from zero (only 3 out of 103 eyes had 95% CIs that did not overlap zero). As such we do not incorporate eye heterogeneity into the model and model pain, burning and photophobia for an average patient.

As with VA we compare model predictions with observed outcomes, table 31. As with VA there is no deterioration of predictive power over time and we therefore adopt the time-invariant model.

**Table 30: Predicted probabilities of pain/burning/photophobia**

| | Baseline with SS | | Baseline w/o SS | | Transplant Failure with SS | | Transplant Failure w/o SS | | Transplant Success with SS | | Transplant Success w/o SS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XB | 2.7899 | | 1.7497 | | 1.8479 | | 0.8077 | | 1.0402 | | 0 | |
| Pain/Burning/Photophobia | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** | Cum Prob | **Prob** |
| None | 57.47% | **57.47%** | 79.27% | **79.27%** | 77.61% | **77.61%** | 90.75% | **90.75%** | 88.60% | **88.60%** | 95.65% | **95.65%** |
| Mild | 85.95% | **28.47%** | 94.54% | **15.27%** | 94.01% | **16.40%** | 97.80% | **7.05%** | 97.24% | **8.63%** | 99.01% | **3.35%** |
| Moderate | 99.44% | **13.49%** | 99.80% | **5.26%** | 99.78% | **5.77%** | 99.92% | **2.13%** | 99.90% | **2.67%** | 99.97% | **0.96%** |
| Severe | 100.00% | **0.56%** | 100.00% | **0.20%** | 100.00% | **0.22%** | 100.00% | **0.08%** | 100.00% | **0.10%** | 100.00% | **0.03%** |

**Table 31: comparison of predicted and observed pain/burning/photophobia over time**

| **PBP** | **Baseline** | | **Year 1** | | **Year 2** | | **Year 3** | | **Year 4** | | **Year 5** | | **Year 6** | | **Year 7** | | **Year 8** | | **Year 9** | | **Year 10** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** | **Obs** | **Pred** |
| **None** | 63 | 60 | 86 | 87 | 60 | 61 | 47 | 46 | 29 | 31 | 16 | 15 | 8 | 7 | 6 | 5 | 5 | 5 | 0 | 1 | 1 | 1 |
| **Mild** | 19 | 26 | 14 | 10 | 6 | 6 | 3 | 3 | 5 | 3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Moderate** | 17 | 13 | 0 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Severe** | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

### 5.3.3 The relationship between transplant success, keratoplasties and stromal scarring

HLSTM01 data also contained dates and outcomes of additional surgery including keratoplasty operations. These dates were matched to data over time to determine which outcomes were recorded after a successful keratoplasty. As the eye examinations contain data on stromal scarring it is possible to see the impact of surgery on stromal scarring. In terms of modelling this provides an indirect link (via probability of stromal scarring) between keratoplasty and an impact on VA.

Stromal scarring was defined as a 0/1 dummy variable set to 1 if the observation reported a 'deep' or 'superficial/deep' opacity result in corneal opacity. Identification of stromal scarring was regarded as more accurate at eye examinations at year one and onwards given the 'ubiquitous presence' of superficial opacity in eyes prior to treatment with HOLOCLAR (Rama unpublished). Table 32 shows nearly 80% of eyes having stromal scarring at year one.

**Table 32: Corneal opacity and stromal scarring at year one**

| Stromal Scarring | N | % |
|---|---|---|
| Clear | 9 | 8.74 |
| Superficial | 12 | 11.65 |
| Superficial/Deep | 27 | 26.21 |
| Deep | 55 | 53.40 |

Table 33 shows the random effects logistic regression results show the probability of the presence of stromal scarring (defined as corneal opacity as being superficial/deep or deep) as a function of the eye random-effect, transplant success and whether the observations comes after a successful keratoplasty on the relevant eye is recorded in the patient record.

**Table 331: Regression model of impact of transplant and keratoplasty on the presence of stromal scarring**

| Effect | Level | Estimate | Standard Error | t Value |
|---|---|---|---|---|
| **Intercept** | | -2.0441 | 0.3485 | -5.87 |

| | | | | |
|---|---|---|---|---|
| **Baseline** | Baseline | -0.1963 | 0.439 | -0.45 |
| **Transplant Outcome** | Fail | -0.03876 | 0.5459 | -0.07 |
| **Transplant Outcome** | Success | 0 | . | . |
| **Keratoplasty** | After Successful Keratoplasty | 3.5325 | 0.4068 | 8.68 |
| | | | | |
| **Eye-Level Random Effect** | Std Dev | 2.4088 | 0.7069 | |
| | | | | |
| **-2 Res Log Pseudo-Likelihood** | | 2036.36 | | |
| **Pseudo-AIC** | | 2046.36 | | |
| **Pseudo-BIC** | | 2066.45 | | |

Unlike VA and other ocular symptoms, there is no direct practical or statistically significant impact of stem cell transplant success or failure on the likelihood of stromal scarring being present. The key factor is whether a keratoplasty has been performed. This is only possible if ocular stability has been achieved and therefore can only occur with a successful stem cell transplant.

Table 34 shows the predicted probabilities of stromal scarring under various scenarios. Probabilities are calculated as standard following logistic regression.

$$\Pr(SS = 1) = \frac{e^{x'\beta}}{1 + e^{x'\beta}}$$

As the regression results suggest only the impact of keratoplasty has any significant practical impact on the probability of stromal scarring.

**Table 34: Predicted probabilities of stromal scarring**

| | **Baseline** | **Failed Transplant** | **Successful Transplant** | **Successful Transplant plus successful keratoplasty** |
|---|---|---|---|---|
| XB | -2.2404 | -2.08286 | -2.0441 | 1.4884 |
| No Stromal Scaring | 9.62% | 11.08% | 11.46% | 81.58% |
| Stromal Scaring | 90.38% | 88.92% | 88.54% | 18.42% |

Finally 35 shows the predictive performance of the model over time and shows a close fit that does not decline over time.

**Table 35: Comparison of observed and predicted stromal scarring over time**

| Time | Observed | Predicted |
|---|---|---|
| Baseline | 89 | 89 |
| Year One | 82 | 82 |
| Year Two | 39 | 40 |
| Year Three | 21 | 21 |
| Year Four | 18 | 18 |
| Year Five | 10 | 8 |
| Year Six | 3 | 3 |
| Year Seven | 3 | 3 |
| Year Eight | 3 | 3 |
| Year Nine | 1 | 1 |
| Year Ten | 1 | 1 |

### 5.3.4 Relationship between underling eye heterogeneity and length of follow-up

A final regression model was conducted to supplement the VA at baseline / length of follow-up relationship. We regressed the length of follow-up on the underlying eye random effects for VA, pain/burning/photophobia and stromal scarring. The results shown in table 36 show no relationship between the underlying characteristics of the eye and the length of follow-up. We can therefore be confident that the HOLOCLAR regression results are an artefact of a longer follow-up time of healthier or more favourable eyes.

**Table 36: Relationship between underlying eye status and length of follow-up**

| Variable | Parameter Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| Intercept | 39.49515 | 2.24888 | 17.56 | <.0001 |
| Visual Acuity RE | -0.31647 | 1.22007 | -0.26 | 0.7959 |
| Stromal Scarring RE | 3.96343 | 2.09166 | 1.89 | 0.0610 |
| Pain/Burning/Photophobia RE | 4.09502 | 5.29473 | 0.77 | 0.4411 |

## *5.4 Measurement and valuation of health effects*

The systematic literature review has revealed no studies (either RCTs or observational) which yields a utility score to LSCD or states of LSCD. At this present point in time there are also no data collected from HOLOCLAR patients via generic instruments such as the EQ-5D.

The burden of disease review suggests that utility or utility decrements may be driven by three main sources: loss of visual acuity; pain/burning/photophobia; and by a cosmetic disfigurement. In addition, patients with eye diseases often have a better-seeing eye (BSE) and a worse-seeing eye (WSE) which may independently, or in tandem, contribute to the individual's overall HRQoL. However, the extent to which HRQoL is driven by the sight of either eye is largely unknown and it is therefore challenging to assess the economic argument of a technology which may only improve the visual acuity of one eye, or one eye at a time.

Our approach has therefore been to model each of these individual utility drivers explicitly. There have been two broad approaches to provide values for these elements.

The first is a bespoke Standard Gamble (SG) stated preference exercise on 520 members of the general public conducted by YHEC on behalf of Chiesi which looked at the utility drivers in total and measuring the trade-offs individuals would be willing to make between VA, pain and cosmetic appearance in both unilateral and bilateral cases. This is provided as Appendix 7.

The second approach is to draw from the broader literature the individual components in isolation. Primarily this has been the mapping of VA in either BSE or WSE to an expected utility.

**Health-related quality-of-life data from clinical trials**

None.

**Mapping**

In addition to the systematic literature review, an additional review of the literature was conducted to understand the more general relationship between VA and utility

with special attention being given to literature which had informed the recent 2015 NICE guidance on the use of Aflibercept for treating diabetic macular oedema.(109)

Hirneiss argues that whilst it is acknowledged that there is no clear consensus on what method to use, the convention in economic evaluation has been to use the VA and utility associated with the BSE and references the 2007 guidance on the use of Lucentis® (Ranibizumab, Novartis Pharma, Basel, Switzerland) in neovascular age-related macular degeneration (AMD) published by the National Institute for Health and Clinical Excellence (NICE) as the classic example.(110) However, drawing on a literature review of studies which assessed the quality of life in both best and worst seeing eyes, Hirneiss concludes that 'The WSE appears to have a stronger influence on [vision-related quality of life] VRQoL, than is generally assumed.' And that 'Treatment strategies which focus on the BSE only are likely to underestimate the impact of visual impairment on VRQoL'.(110)

Finger et al in a cross-sectional study using the EQ-5D instrument (NZ VAS weighting) and VisQoL utility index instrument of 1,085 German and Australian patients with visual impairment and 254 control study participants without visual impairment go further.(111) They find that 'contrary to the assumption that the better eye solely or mostly determines vision-related activity limitation, quality of life and utilities, treatment of the better *and* worse eye confers a patient reported benefit.' And that the findings ' from the current study of an additional impact of worse eye VA on reported utilities combined with the above evidence that improvements in utilities and VRQoL are often irrespective of better or worse eye treatment, suggest that resource allocation and treatment decisions should not be based on better eye VA only.' They especially draw attention to cases where the BSE has good VA; 'Our data show that determination of vision-related utility values should be guided by VA in both eyes with specific attention given to the worse eye in cases with good seeing better eyes.' And their strong conclusion is that 'calculating utilities based only on better eye VA is likely to underestimate the impact of vision impairment, in particular when the better eye functions well and the other (worse) eye is moderately or severely visually impaired. These findings have considerable implications for defining visual impairment, for economic evaluations within eye health as well as for treatment decisions, as the conventional maxim "still got one good eye" is likely to

not reflect patients' preferences and underestimate the impact of poor vision in either eye.' We note that their conclusions are driven by responses to the VisQoL instrument rather than the EQ-5D which showed no systematic variation across either BSE or WSE.

Other studies using non-generic measures generally agree with the Hirneiss and Finger et al conclusions that unilateral impairment has an impact on health related quality of life. For example Vu et al using a cluster stratified random sample of 3,271 urban participants recruited between 1992 and 1994 for the Melbourne Visual Impairment Project, find that 'both unilateral and bilateral vision loss were significantly associated with increased odds of having problems in visual functions including reading the telephone book, newspaper, watching television, and seeing faces.(112) Non-correctable by refraction unilateral vision loss increased the odds of falling when away from home (OR=2.86, 95% CI 1.16 to 7.08), getting help with chores (OR=3.09, 95% CI 1.40 to 6.83), and becoming dependent (getting help with meals and chores) (OR=7.50, 95% CI 1.97 to 28.6).'

A study of the 9,330 participants of 1958 British Cohort study at ages 44-45 by Rahi et al found that patients with unilateral visual impairment (n = 1098) had a statistically significant higher odds ratio (2.94) of reporting a VRQoL score equal to or in excess of 2 (where higher scores reflect lower quality of life) relative to the general population without any visual impairment.(113)

Reporting on the Corneal Opacity Rural Epidemiological (CORE) study of 12 899 participants from 25 randomly selected clusters of rural India, Vashist et al found that patients with unilateral corneal disease also had poorer VR-QoL scores as compared with healthy controls ($p<0.0001$).(114)

However results using generic measures or stated preference techniques have not been so clear cut.

With 996 telephone interviews of patients with subfoveal choroidal neovascularisation patients, Bass found 'As one of the largest studies of preference values in patients with eye disease, this investigation has shown convincingly that patients with subfoveal CNV in one eye, with or without a neovascular lesion in the fellow eye, assign low preference values to their health status … the impact is

greatest in those with the most severe loss of vision, but even patients with visual acuity of at least 20/40 in 1 eye had relatively low preference values.'(115)

However a seminal article by Brown et al critically found mixed results regarding a systematic relationship between TTO derived utilities and VA in the WSE.(116) Using 81 patients with good VA in one eye and 66 patients with good VA in both eyes they elicited utility values via a TTO exercise which asked for life years willing to be sacrificed in order to guarantee perfect vision in both eyes for the remaining duration of life. Overall they found that the mean time trade-off utility value in 81 patients with good visual acuity in one eye was 0.89 (standard deviation, 0.17; 95% confidence interval, 0.85–0.93), whereas the mean value in 66 patients with good vision in both eyes was 0.97 (standard deviation, 0.05; 95% confidence interval, 0.97–0.99), thus indicating that utility was not solely a function of the BSE. However when stratifying results according to WSE they found 'no obvious correlation between decreasing vision in the poorer-seeing eye and mean utility values.' The results are shown 37.

**Table 37: Brown et al utility in WSE**(116)

| Vision in Poorer Eye | N | Mean Utility Value | Standard Deviation | 95% CI |
|---|---|---|---|---|
| Better than 20/40 | 66 | 0.97 | 0.05 | 0.97 – 0.99 |
| 20/40 – 20/50 | 24 | 0.87 | 0.16 | 0.81 – 0.93 |
| 20/70 – 20/100 | 12 | 0.9 | 0.16 | 0.81 -0.99 |
| 20/200 – 20/400 | 14 | 0.94 | 0.13 | 0.81 – 1.00 |
| CF - LP | 25 | 0.88 | 0.18 | 0.81 – 0.95 |
| No LP | 6 | 0.81 | 0.16 | 0.65 – 0.97 |

Taken at face value it implies that unless a technology can effectively restore a WSE to near perfect visual acuity then there is no utility to be gained from fairly significant improvements in VA in the WSE i.e. improving VA in the WSE from LP to 20/40 implies a utility decrease of 0.01 – a counter intuitive finding. The authors appear cautious about their findings and are conservative in their conclusions – 'it is uncertain whether worsening vision in the poorer-seeing eye is associated with a decreasing, or some other, trend in utility values.' And possibly mindful of the low sample numbers, they also state that additional data will be necessary to definitively

address this question. Their main conclusion remains that 'good vision in two eyes confers a substantially higher quality of life to patients with ocular diseases than does good vision in only one eye from the patient preference-based perspective.' Nevertheless it is possible that the finding of a lack of obvious relationship between WSE and utility in this study has influenced future research by these influential authors and their collaborators which have almost exclusively focussed on assigning utility values to BSE only.(117,118)

Other papers by Brown may compound this issue by employing a methodology which overemphasises the role of BSE in determining utility. For example, TTO methods used on patients with eye disease by Brown et al (1999 record data and classify results by BSE only despite the scenarios presenting a time-trade off of perfect vision being restored in *both eyes.*(119) Thus whilst it is possible to measure the improvement in VA of the BSE being offered in the scenario to an individual respondent there is also an implied, but unmeasured, improvement in the VA of the WSE too. And by definition the improvement in the VA of the WSE to perfect vision must be at least as big as, and probably greater than, the improvement in the VA of the BSE. This issue will be potentially greater the higher the initial starting value of BSE VA as mathematically it may mask a greater range of WSE VA. It is therefore likely that these data which link BSE VA to utility are biased.

Thus the current perceived wisdom, at least from an economic evaluation perspective, appears to be that there is little evidence regarding the relationship between WSE and utility, specifically that worsening WSE, all other things being equal, may have little or no impact on overall health-related quality of life. However this message seems mainly to be driven by one small scale study albeit by influential authors. Though it should be noted that they seem to downplay the significance of that particular element. All the other reviewed evidence, although also limited, suggests a positive correlation, notably Finger et al(111), which we explore in more depth.

Table 38 shows the VisQoL utilities from Finger et al (2013).

**Table 38: Finger et al VisQoL utilities**(111)

| BSE\WSE | BSE only | No impairment | Mild | Moderate/severe |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| No impairment (VA >0.5) | 0.92 ± 0.13 (n=577) | 0.95 ± 0.1 (n=371) | 0.90 ± 0.16 (n=111) | 0.86 ± 0.17 (n=95) |
| Mild (VA 0.32 – 0.5) | 0.84 ± 0.18 (n=102) | | 0.85 ± 0.17 (n=32) | 0.84 ± 0.19 (n=70) |
| Moderate/Severe (VA < 0.32) | 0.71 ± 0.28 (n=128) | | | 0.71 ± 0.28 (n=128) |
| WSE only | | 0.95 ± 0.1 (n=371) | 0.89 ± 0.17 (n=143) | 0.79 ± 0.24 (n=293) |

Finger et al suggest that in the absence of utility data collected from patients then a reasonable compromise might be to use a table similar to that reported above.(111) We agree that this is an appealing alternative to Brown et al(116) in that it more closely agrees with the broader literature, is based on a far larger sample size and is conducted in a more recent sample. There is however an issue with coverage and the wide definition of the moderate/severe state which covers a wide range of possible VA such that the mean values may not be very representative of severe VA scores which patients tend to present with LSCD.

A potential solution to this problem is to use the Finger et al(111) data to understand the relationship between BSE and WSE states and applying it to VA/utility algorithms that have been used elsewhere. A variant of this approach was used in the 2015 NICE guidance on the use of Aflibercept for treating diabetic macular oedema, where a (seemingly arbitrary) proportionate 77% weighting was applied to the BSE VA and a 23% weighting applied to a WSE read from the table as if it were the BSE.(109) These proportions were applied to the Czoski-Murray et al VA to utility algorithm to determine overall utility from differing BSE/WSE combinations as the base case scenario.(120)

We adopt a similar approach, but we use the Finger et al study(111) to try and derive an empirical measure of the relationship between BSE VA, WSE VA and utility as well as allow the 23% weighting as a sensitivity analysis.

The relationship between BSE VA and WSE VA in the Finger et al study(111) is estimated by a simple OLS regression model which models BSE/WSE specific reported utility as a function of the BSE only and WSE only average utilities. In order

to ensure that the contributions of each eye sum to 100% we restrict the OLS to having no intercept and that the coefficients of BSE and WSE sum to 1. Thus we may regard the coefficients attached to each variable as the proportion of that eye's VA to overall utility. For example and referring back to Table 19, we model the utility of a BSE mild - WSE moderate/severe combination (0.84) as a function of the average of BSE mild utility (0.84) and WSE moderate/severe utility (0.79).

We note that in the original Finger et al(111) data sometimes the average utility of the BSE seeing eye is lower than that recorded for the average of the WSE, this is more likely when the BSE and WSE eyes are of the same category. This is not surprising as setting the WSE level automatically imposes a minimum level for the BSE whereas setting a BSE level imposes no such minimum level for WSE.

In the BSE/WSE model we leave the data as it is and regress combined utility on that reported for BSE and WSE respectively. As an alternative we create a highest/lowest utility model whereby the highest [lowest] utility value is recorded as the highest [lowest] value between the BSE and WSE averages and we regress combined utility on the highest and lowest recorded utilities.

Table 39 and Table 40 show the data set-up for two alternative models.

**Table 39: BSE/WSE model**

| N | Analytical Weight | BSE Utility | WSE utility | Combined utility |
|---|---|---|---|---|
| 371 | 0.460 | 0.92 | 0.95 | 0.95 |
| 111 | 0.138 | 0.92 | 0.89 | 0.9 |
| 95 | 0.118 | 0.92 | 0.79 | 0.86 |
| 32 | 0.040 | 0.84 | 0.89 | 0.85 |
| 70 | 0.087 | 0.84 | 0.79 | 0.84 |
| 128 | 0.159 | 0.71 | 0.79 | 0.71 |

**Table 40: Highest/Lowest model**

| N | Analytical Weight | highest utility | lowest utility | Combined utility |
|---|---|---|---|---|
| 371 | 0.460 | 0.95 | 0.92 | 0.95 |
| 111 | 0.138 | 0.92 | 0.89 | 0.9 |
| 95 | 0.118 | 0.92 | 0.79 | 0.86 |

| | | | | |
|---|---|---|---|---|
| 32 | 0.040 | 0.89 | 0.84 | 0.85 |
| 70 | 0.087 | 0.84 | 0.79 | 0.84 |
| 128 | 0.159 | 0.79 | 0.71 | 0.71 |

In both cases in order to attach more analytical weight to the cells with greater volumes of responders we attach an analytical weight to each cell which is in proportion to the overall sample size. So for example the contribution of no impairment in either eye to the regression likelihood is over 5 times that of mild – moderate/severe reflecting the fact that there are over 5 times the same size in the no impairment combination cell.

Table 41 shows the regression results for both models. The original BSE/WSE model has a marginally better fit in terms of root mean squared error and represents more conservative results, we thus adopt those results as our base case measure of the relationship between BSE, WSE and overall utility.

**Table 41: Combined utility as a function of separate eye utilities**

| | **BSE/WSE model** | | **Highest/Lowest Utility Model** | |
|---|---|---|---|---|
| | **Estimate** | **Std Err** | **Estimate** | **Std Err** |
| **BSE utility / Highest utility** | 0.628 | 0.137 | 0.457 | 0.147 |
| **WSE utility / Lowest utility** | 0.372 | 0.137 | 0.543 | 0.147 |
| | | | | |
| **Adj R Squared** | 0.9994 | | 0.9994 | |
| **Root MSE** | 0.00852 | | 0.00916 | |

The regression model appeals to the underlying rationale of the table: If WSE makes no contribution to overall utility we would expect to see no variation across the rows of the cells. Similarly in a regression model, if WSE makes no contribution to overall utility then the estimated coefficient attached to WSE would be zero, or not statistically significant from zero. Both models reject the null hypothesis that the WSE/lowest utility eye makes no contribution.

We may then apply these estimated relationships to tables of BSE VA to utility maps such as Czoski-Murray et al(120), Brown et al(118) and Brown et al(117) to obtain utilities from specific BSE/WSE combinations. As an example we apply the

BSE/WSE model to the Czoski-Murray et al(120) TTO values for simulated ARMD states as shown in table 42.

**Table 42: BSE and WSE VA combinations and implied utility from Czoski-Murray et al**(120) **group means**

| BSE | WSE | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 | 0.1 | CF | HM | LP | NLP |
| 1 | 0.706 | 0.706 | 0.706 | 0.706 | 0.706 | 0.697 | 0.697 | 0.697 | 0.634 | 0.634 | 0.634 | 0.561 | 0.561 | 0.561 |
| 0.9 | | 0.706 | 0.706 | 0.706 | 0.706 | 0.697 | 0.697 | 0.697 | 0.634 | 0.634 | 0.634 | 0.561 | 0.561 | 0.561 |
| 0.8 | | | 0.706 | 0.706 | 0.706 | 0.697 | 0.697 | 0.697 | 0.634 | 0.634 | 0.634 | 0.561 | 0.561 | 0.561 |
| 0.7 | | | | 0.706 | 0.706 | 0.697 | 0.697 | 0.697 | 0.634 | 0.634 | 0.634 | 0.561 | 0.561 | 0.561 |
| 0.6 | | | | | 0.706 | 0.697 | 0.697 | 0.697 | 0.634 | 0.634 | 0.634 | 0.561 | 0.561 | 0.561 |
| 0.5 | | | | | | 0.681 | 0.681 | 0.681 | 0.618 | 0.618 | 0.618 | 0.545 | 0.545 | 0.545 |
| 0.4 | | | | | | | 0.681 | 0.681 | 0.618 | 0.618 | 0.618 | 0.545 | 0.545 | 0.545 |
| 0.3 | | | | | | | | 0.681 | 0.618 | 0.618 | 0.618 | 0.545 | 0.545 | 0.545 |
| 0.2 | | | | | | | | | 0.511 | 0.511 | 0.511 | 0.438 | 0.438 | 0.438 |
| 0.1 | | | | | | | | | | 0.511 | 0.511 | 0.438 | 0.438 | 0.438 |
| CF | | | | | | | | | | | 0.511 | 0.438 | 0.438 | 0.438 |
| HM | | | | | | | | | | | | 0.314 | 0.314 | 0.314 |
| LP | | | | | | | | | | | | | 0.314 | 0.314 |
| NLP | | | | | | | | | | | | | | 0.314 |

Figures in the diagonal running from the top left to the bottom right represent the original figures as grouped by BSE VA from Czoski-Murray et al.(120) Overall utility from specific combinations may be identified by identifying BSE VA in the row with WSE VA from the column. For example, a BSE VA of 0.5 with a WSE VA of HM would yield a utility of 0.545.

The Czoski-Murray et al(120) results are a useful benchmark as they have frequently been used in NICE evaluations and therefore have set a precedent of use and allow comparison across treatments.(109) However more than that, the novel technique they use of applying custom-made contact lenses to simulate VA impairment to otherwise healthy members of the general public has appealing qualities for the proportion based approach to generating combinations of BSE and WSE from BSE grouped tables. Firstly they isolate the impact of VA on utility from other factors which may be disease specific, i.e. there are no other influences correlated with VA that might contaminate utility derived from a patient population. As Brown et al(116) note, it is ‘the degree of visual loss itself, rather than the cause of the visual loss,

[which] appears to correlate with the utility value', thus it would appear reasonable to use these utilities to account for the impact of VA impairment in isolation. The other large benefit of using the Czoski-Murray et al(120) experiment is that as they used the same contact lenses in each eye then there is greater assurance of a stronger (though not perfect) correlation of VA between the BSE and the WSE. Whilst this may not seem important, there would appear to be an underlying implicit assumption in the conversion of BSE based tables to BSE/WSE combinations that requires us to be able to meaningfully apply any proportion algorithm. The assumption being that the value we have for any given BSE VA represents a BSE/WSE combination of the same VA. The Czoski-Murray et al(120) data probably represent the closest we get to that assumption.

In order to assess the sensitivity of our results to alternative quality of life mappings we consider the following in addition to our base case:

- The Czoski-Murray et al(120) model 1 regression results for simulated TTO
- Brown et al(117)
- Brown et al(118)

**Table 43: Alternative VA - Utility mappings**

| Visual Acuity | Czoski-Murray et al (2009) – TTO simulated Group Means | Czoski-Murray et al (2009) – TTO simulated OLS model | Brown et al (2008) | Brown et al (2003) |
|---|---|---|---|---|
| 1 | 0.706 | 0.828 | 0.970 | 0.880 |
| 0.9 | 0.706 | 0.812 | 0.920 | 0.880 |
| 0.8 | 0.706 | 0.793 | 0.870 | 0.880 |
| 0.7 | 0.706 | 0.772 | **0.848** | 0.810 |
| 0.6 | 0.706 | 0.748 | 0.824 | 0.810 |
| 0.5 | 0.681 | 0.720 | 0.800 | 0.810 |
| 0.4 | 0.681 | 0.685 | 0.770 | 0.810 |
| 0.3 | 0.681 | 0.640 | **0.744** | 0.720 |
| 0.2 | 0.511 | 0.577 | 0.670 | 0.720 |
| 0.1 | 0.511 | 0.469 | 0.660 | 0.610 |

| | | | | |
|---|---|---|---|---|
| CF | 0.511 | 0.110 | 0.520 | 0.610 |
| HM | 0.314 | **0.110** | 0.350 | 0.610 |
| LP | 0.314 | **0.110** | 0.350 | 0.610 |
| NLP | 0.314 | **0.110** | 0.260 | 0.610 |

Figures in bold are imputed. For example the Czoski-Murray et al(120)regression model predicted implausibly large negative values for states HM and below. We replace them with the value for CF. For Brown et al(117) the figures are based on a weighted average conversion of distance VA scores to decimal VA scores.

**Health-related quality-of-life studies**

A sample of 520 adult members of the population were recruited by a third party (Qualtrics) and presented with 12 SG questions. Although non-random the sample is broadly representative of the UK population.

In each question respondents were presented with a choice between two alternatives where in one scenario the health state is certain and in the other there is the option of the best possible health state but an element of risk, death in this case. With anchor points of perfect health as one and death as zero on the utility scale, then the amount of risk a respondent is willing to undertake reveals the utility attached to that specific state.

Of the 12 questions posed the first four referred to the unilateral case whereby normal sight, pain and cosmetic appearance may be returned to normal (i.e. normal VA, no pain and no disfigurement) in both eyes. The remaining 8 scenarios referred to a bilateral situation with a combination of poor VA in one eye and moderate VA in other (pain and disfigurement in both eyes) where normality may be returned to one eye only. In questions 5 to 8 the eye with moderate VA impairment was treated and in questions 9 to 12 the eye with poor VA is treated.

Moderate VA was defined as having difficulty reading and identifying obstacles whilst moving around; poor VA as being near blind, being able only to identify light and shadows and perceive movement. Pain was defined as ‘a burning pain with sensitivity to light’ and disfigurement was illustrated by closely cropped photos of eyes with moderate and total LSCD.

Table 44 shows the mean implied utility value derived from the standard gamble experiment.

**Table 44: Standard Gamble mean utilities**

| Scenario | Pre-treatment scenario | Treatment scenario | SG Utility Mean (95% CI) |
|---|---|---|---|
| 1 | LSCD in one eye, causing poor vision, disfigurement, and pain with photophobia. | Restores vision to a moderate level and removes the pain with photophobia. | [redacted] |
| 2 | | Removes disfigurement and the pain with photophobia. | [redacted] |
| 3 | | Restores vision to normal and removes disfigurement. | [redacted] |
| 4 | | Restores vision to near normal and removes the pain with photophobia. | [redacted] |
| 5 | LSCD in both eyes, causing vision to be poor in one eye and moderate in the other, and causing disfigurement and pain with photophobia in both eyes.<br><br>Only the eye with moderate vision is treated. | Removes the pain with photophobia in eye with moderate vision. | [redacted] |
| 6 | | Removes disfigurement and the pain with photophobia in the eye with moderate vision. | [redacted] |
| 7 | | Restores vision to near normal, and removes disfigurement and the pain with photophobia in the eye with moderate vision. | [redacted] |
| 8 | | Removes disfigurement and the pain with photophobia in the eye with moderate vision. | [redacted] |
| 9 | LSCD in both eyes, causing vision to be poor in one eye and moderate in the other, and causing disfigurement and pain with photophobia in both eyes. | Restores vision to a moderate level and removes the pain with photophobia in the eye with poor vision. | [redacted] |

| Scenario | Pre-treatment scenario | Treatment scenario | SG Utility Mean (95% CI) |
|---|---|---|---|
| 10 | Only the eye with poor vision is treated. | Removes disfigurement and the pain with photophobia in the eye with poor vision. | [redacted] |
| 11 | | Restores vision to near normal and removes the disfigurement and the pain with photophobia in the eye with poor vision. | [redacted] |
| 12 | | Restores vision to near normal and removes the disfigurement in the eye with poor vision. | [redacted] |

Overall average utilities for the different scenarios were [redacted] and the highest utility means [redacted]

There are however some paradoxical results in the responses. In each of the bilateral sets of scenarios whether it be the poorest seeing eye treated (questions 9 to 12) or the better seeing eye treated (questions 5 to 8 inclusive) there is an option which if we can assume that no pain is no worse than some pain, that no disfigurement is no worse than some disfigurement and normal or near normal vision is no worse than either moderate or poor vision should have the highest utilities. They are questions 7 and 11 respectively. As they restore full health to the treated eye then, under the previous assumptions, they should yield a utility that is no lower (and indeed we would expect higher) than the other 3 questions in that set of scenarios which only restore health in some but not all of the 3 dimensions. However, [redacted]. Further exploration of the data reveals [redacted]

We run separate regression models on scenarios 1 to 4 and then 5 to 12 to attempt to understand the individual contributions to the reported mean utility level. We regressed individual level responses measured as a utility decrement from 1 in both cases on a set of variables as implied by the scenario options.

In the unilateral model no pain, no disfigurement and normal VA in both eyes is assumed a utility decrement of zero. Deviations from this baseline include moderate or poor VA in the WSE and the presence of pain and disfigurement. An Ordinary Least Squares model without an intercept is estimated and shown in Table 45.

**Table 45: Unilateral LSCD scenarios and estimated utility decrements**

| Variable | Parameter Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| BSE = Normal Vision WSE = Moderate VA | [redacted] | [redacted] | [redacted] | [redacted] |
| BSE = Normal Vision WSE = Poor VA | [redacted] | [redacted] | [redacted] | [redacted] |
| Pain in WSE | [redacted] | [redacted] | [redacted] | [redacted] |
| Disfigurement in WSE | [redacted] | [redacted] | [redacted] | [redacted] |

The results show that, [redacted] These are of similar but slightly larger magnitudes indicating [redacted]

Table 46 shows the regression results for data from scenarios 5 through 12. The baseline here is BSE equals Normal Vision and WSE equals Moderate VA with pain and disfigurement in one eye only. This time an intercept was included in the model to reflect the fact that perfect health in both eyes is not attainable in the choice sets.

**Table 46: Bilateral LSCD scenarios utility decrements**

| Variable | Parameter Estimate | Standard Error | t Value | Pr > \|t\| |
|---|---|---|---|---|
| Intercept | [redacted] | [redacted] | [redacted] | [redacted] |
| BSE = Normal Vision WSE = Poor VA | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| BSE = Moderate VA WSE = Moderate VA | [redacted] | [redacted] | [redacted] | [redacted] |
| BSE = Moderate VA WSE = Poor VA | [redacted] | [redacted] | [redacted] | [redacted] |
| BSE = Poor VA WSE = Poor VA | [redacted] | [redacted] | [redacted] | [redacted] |
| Pain in Both Eyes | [redacted] | [redacted] | [redacted] | [redacted] |
| Disfigurement in Both Eyes | [redacted] | [redacted] | [redacted] | [redacted] |

As perhaps expected given the discussion of the paradoxical overall means the results are slightly counterintuitive. The intercept term captures the utility decrement of BSE having normal vision and WSE having poor VA with pain and disfigurement. [redacted] The table also suggests that [redacted] The other substantive result from the regression model is [redacted].

In conclusion the SG exercise conducted on 520 representative members of the public has led to limited insight. The responses to scenarios 5 to 12 which looked at the bilateral scenarios appear to yield results [redacted]. As such it is difficult to draw any strong conclusions from this data.

The analysis of the unilateral scenarios (1 through 4) represents a simpler exercise, table 47, and the results seem plausible. Analysis on this data does appear to yield some insight. Whilst the impact of a declining VA in the WSE on utility [redacted] there is compelling evidence that respondents [redacted]. As such the following associated utilities may be used to drive an economic model based on VA, pain and cosmetic appearance.

**Table 47: YHEC SG implied model parameters**

| BSE/WSE VA ; Pain ; Disfigurement | Utility Decrement |
|---|---|
| BSE = Normal Vision WSE = Normal Vision | [redacted] |
| BSE = Normal Vision WSE = Moderate VA | [redacted] |
| BSE = Moderate VA WSE = Moderate VA | [redacted] |
| BSE = Normal Vision WSE = Poor VA | [redacted] |
| BSE = Moderate VA WSE = Poor VA | [redacted] |
| BSE = Poor VA WSE = Poor VA | [redacted] |
| Pain in any eye | [redacted] |
| Disfigurement in any eye | [redacted] |

The full report of the Standard Gamble study is provided as Appendix 7.

**Adverse reactions**

Section 4.12 reports inconsistent and incomplete recording of safety events across the observational studies. Drawing definitive conclusions on absolute and relative risk from the literature is therefore not possible.

Expert opinion,(57) drew firmer conclusions on the probability of Glaucoma in particular stating rates of 5% for CLAU and 10% each for lr-CLAL and KLAL. For HOLOCLAR, the current approved SmPC records a rate of 3.5%

Based on Fielding et al(109) a utility decrement of 0 is assumed, though there are cost consequences.

**Health-related quality-of-life data used in the model**

Table 48 shows the VA utilities associated with each model state in combination with presence or absence of stromal scarring, the expected presence of pain and disfigurement. Pain is a probabilistic function of model states as shown in table 30 whereas disfigurement is assumed present under all states except stable without stromal scarring. Utilities are assumed constant over time.

**Table 48: Summary of utilities associated with model states**

| State | VA based Utility | Pain/Burning/ Photophobia | Disfigurement | Overall Utility |
|---|---|---|---|---|
| Baseline with stromal scarring | 0.56 | -0.019 | -0.318 | 0.223 |

| | | | | |
|---|---|---|---|---|
| Baseline without stromal scarring | 0.6 | -0.007 | -0.318 | 0.275 |
| Transplant failure/ BSC with stromal scarring | 0.57 | -0.008 | -0.318 | 0.244 |
| Transplant failure/BSC without stromal scarring | 0.63 | -0.003 | -0.318 | 0.309 |
| Transplant success/Stable with stromal scarring | 0.6 | -0.004 | -0.318 | 0.278 |
| Transplant success/Stable without stromal scarring | 0.67 | -0.001 | 0 | 0.669 |
| Dead | 0 | | | 0 |

## *5.5 Cost and healthcare resource use identification, measurement and valuation*

**Resource identification, measurement and valuation studies**

Resource use was identified through a targeted review of the literature which was supplemented with expert opinion.

**Intervention and comparators' costs and resource use**

This section details the resource use and costs associated with HOLOCLAR and the other procedures. This can be separated into two parts, the resource use and costs associated with the initial biopsy and the resource use and costs associated with the main implantation and inpatient stay. For Holoclar, the unit cost used in the base case is the patient access scheme (simple discount scheme) price referred to PASLU for inclusion in this submission.

*Biopsy*

For the biopsy, patients are expected to undergo the procedure and then receive ongoing treatment with antibiotic eye drops, steroid eye drops and artificial tears for two weeks until the peripheral cornea has re-epithilised.(10) Patients are expected to use each of the eye drops 4 times a day for 2 weeks, costs for each of these are detailed in table 1. If nylon sutures are used, patients will have to undergo another procedure after 2 weeks to remove them. For each procedure a cost of £675 is incurred (based on NHS reference cost for a Minor Cornea or Sclera elective procedure).

*Main implantation and inpatient stay*

For the main transplant, patients are expected to undergo the procedure but not have any extended stay in hospital. The cost for the main transplant is £2934.30 (based on NHS reference cost for Very Complex, Cornea or Sclera Procedures with CC Score 0-1). For lr-CLAL and CLAU an amniotic membrane is used during the transplant, for KLAL two membranes are used, whereas for HOLOCLAR none is used. Patients will also have a bandage contact lens applied by the ophthalmologist to protect the eye.(37)

**Health-state unit costs and resource use**

The de novo economic model includes health states for the initial year following the successful surgery, subsequent years following a successful surgery and the transplant remaining stable and failures and best supported care. The resource use associated with each of these states is detailed below.

*Stable first 12 months: Post-operative care in the year following successful transplant procedure*

After the transplant and inpatient stay, patients are expected to receive increased care in the year following the procedure. For the first 2 months patients will be treated with antibiotic eye drops, steroid eye drops, artificial tears and a course of autologous serum eye drops.(35,121) Eye drops are used 4 times per day.

During the first year patients will also attend outpatient ophthalmologist appointments, with appointments weekly for the first 2 months, then fortnightly up to month 6 and finally monthly up to 12 months for a total of 22 visits during the year.

Patients receiving KLAL and lr-CLAL will also undergo treatment with immunosuppressants. In the base case this treatment was assumed to continue for the first year. However, as a scenario analysis, this treatment continued until failure of the transplant.

*Stable 12 months plus*

Following a successful transplant, it is assumed that one year after surgery patients will require no ongoing treatment for their eye.

*Failure / Best supportive care*

Patients whose transplant fails or who never undergo a transplant will receive best supportive care. This includes regular ophthalmology outpatient appointments (6 per year) and ongoing treatment with antibiotic eye drops, steroid eye drops and artificial tears. Further, it is expected that these patients will have two flare ups per year which will require extra treatment with autologous serum eye drops and a course of oral antibiotics.(57) The impact of varying the number of flare ups whilst on best supported care is considered as a scenario analysis.

### Adverse reaction unit costs and resource use

Glaucoma is costed at £1,151 by Fielding et al.(109)

### Miscellaneous unit costs and resource use

One year after a successful surgery some patients (56.84%) will be able to undergo a keratoplasty procedure. The cost for the keratoplasty procedure is £2934.30 (based on NHS reference cost for Very Complex, Cornea or Sclera Procedures with CC Score 0-1). Following their inpatient stay, patients will also receive treatment with antibiotic eye drops, steroid eye drops and artificial tears for 2 months.

### Table 49: Full list of costed components

| Resource use item | Unit Cost | Source and extra details |
|---|---|---|
| **Product Costs** | | |
| HOLOCLAR | [redacted] | Patient access scheme (simple discount scheme) price referred to PASLU for inclusion in this submission |
| CLAU | £ - | |
| Ir-CLAL | £ - | |
| KLAL | £ 1,056.53 | Assume same cost as Cornea |
| Cornea | [redacted] | Single Cornea [redacted] NHS Blood and Transplant |
| Amniotic membrane | [redacted] | Frozen Amniotic Membrane 2x2cm [redacted] NHS Blood and Transplant |
| **Surgery Costs** | | |
| Biopsy Procedure cost | £ 675.73 | RC: Minor, Cornea or Sclera Procedure for Biopsy |
| Surgery Procedure cost | £ 2,934.30 | RC: Very complex, Cornea or Sclera Procedures with CC Score 0-1 (1.43 days in hospital) |
| Outpatient appointments | | |
| Ophthalmology outpatient appointment | £ 60.13 | RC: Average cost of a medical ophthalmology outpatient appointment |
| **Medication** | | |
| Steroid Eye Drops | £ 0.01 | MIMs Online Prednisolone sodium phosphate 0.5% 10ml £2- 100 drops |

| | | |
|---|---|---|
| Antibiotic Eye Drops | £ 0.01 | MIMs Online Chloramphenicol 0.5% 10ml £1.45 |
| Artificial Tears | £ 0.04 | MIMs Online Carmellose Sodium 0.5% 10mL |
| Autologous Serum Eye Drops | [redacted] | NHS Blood and Transplant |
| Immunosuppression | £ 1.20 | MIMs Online Ciclosporin 50mg 30-cap pack = £35.97 |
| Oral antibiotics | £ 0.09 | MIMs Online Oral Tetracycline 28 packet £2.62 |
| Oral antibiotics- Doxy | £ 3.01 | MIMs Online Oral doxycycline 2 weeks of treatment |
| Oral prednisolone | £ 10.83 | MIMs Online £10.83 for 4 weeks |
| Topical dexamethasone | £ 13.58 | MIMs Online Topical dexamethasone 4 weeks of treatment |
| **Contact Lenses** | | |
| Bandage Contact Lens | £ 4.17 | http://www.visiondirect.co.uk/purevision |
| **Adverse Events** | | |
| Glaucoma | £ 1,151 | From NICE Aflibercept for treating diabetic macular oedema (Fielding et al 2014) |

## *5.6 Summary of base-case de novo analysis inputs and assumptions*

**Summary of base-case de novo analysis inputs**

The base case model assumes a male patient with an average of 46 as representative of the HLSTM01 patient population. A lifetime duration is used (allowing for mortality) and discount rates of 1.5% for both costs and utilities are applied on the basis that the technology has prolonged effect (over 30 years) and can return patients to a high utility state.

All transplant options start with a biopsy. In all cases the assumed success rate is 100% except for HOLOCLAR where a 90% success rate is assumed.

Transplant success rates for CLAU, Ir-CLAL and KLAL are based on the systematic literature review, as described in table 14. In the absence of the ability to do a formal network analysis due to a consistent lack of control groups, a simple pooling of individual trials provides the basis for the value for each. These initial rates of success are 87% for CLAU, 95% for Ir-CLAL and 94% for KLAL.

The model permits selection of individual study results and/or expert opinion as alternatives.

For HOLOCLAR initial and follow-up transplant success rates were taken from the HLSTM01 trial. These rates are 68% and 75% respectively.

In all cases of estimated initial transplant success rates a Beta distribution was used to capture uncertainty with parameters α and β derived from the raw number of success and failures, table 50.

**Table 50: Transplant success and survival rates**

| Transplant | % | Distribution | Alpha | Beta |
|---|---|---|---|---|
| HOLOCLAR Biopsy | 90 | | | |
| All other Biopsy rates | 100 | | | |
| HOLOCLAR (initial transplant) | 68% | Beta | 73 | 34 |
| HOLOCLAR (second/third transplant) | 75% | Beta | 9 | 3 |
| CLAU | 87% | Beta | 138 | 21 |
| Lr-CLAL initial | 95% | | | |
| Lr-CLAL annual survival | 92% | | | |
| KLAL initial | 94% | | | |
| KLAL annual survival | 77% | | | |
| HOLOCLAR re-operation rate | 35% | | | |
| CLAU re-operation rate | 0% | | | |
| Lr-CLAL re-operation rate | 0% | | | |
| KLAL re-operation rate | 100% | | | |

In the event of a transplant failing for HOLOCLAR and KLAL options a further two operations are allowed. For CLAU and lr-CLAL the base case assumes no further opportunity of transplant. The base case assumes the HLSTM01 observed re-operation rate of 35% and for KLAL 100% which may be applied up to a maximum of 3 operations.

For autografts CLAU and HOLOCLAR the evidence shows that all failures occur in the first year and the survival of the transplant is modelled as that at the end of the first year for future time periods. For the allografts there is compelling evidence that the rate of failure continues beyond the first year, thus a simple survival model was estimated from the literature. To estimate the survival rates from this data, the probability of failure over the mean follow up was calculated. The failure rate for each study was assumed to be constant over time. Therefore, an exponential distribution was assumed, and the probability over the follow up of each period converted to a rate, adjusted to calculate the annual rate of failure and then converted back to an annual probability. For each procedure, a pooled probability of all studies was calculated based on a weighted average of the probability from each study (with the weight determined by the sample size). For lr-CLAL the base case pooled data gave a 92% probability of transplant surviving each subsequent year and for KLAL a 77% probability.

For BSC without any transplant patients remain in their original state with probability of pain, stromal scarring and baseline distribution of VA.

In all cases all-cause mortality over time is a possibility. We have used standard ONS and gender specific lifetables for this application.

The model predicts a distribution of VA given: the success or failure of transplant; the presence or absence of stromal scarring and an underlying eye specific VA factor. The success or failure of the transplant over time are determined by the parameters discussed above. The presence of stromal scarring is dependent upon the underlying rate within the presenting patient populations (determined as 90% from HLSTM01) and whether a successful keratoplasty has been conducted (at year one). This is conditional on stromal scarring being present within an individual and the presence of a successful transplant at year one. However even then not all patients

will undergo a keratoplasty with this conditional probability being estimated as 57% from HLSTM01. A success rate of 98% is used for Keratoplasty success, which again is derived from the HLSTM01 data. There are three values for underlying eye-specific VA factors -2.30, 0 and +2.30 with population weights 25%, 50% and 25% respectively. These values are taken as the mean values for the lower 25%, middle 50% and highest 25% Empirical Bayesian estimates of the individual constant terms estimated in the ordered logistic regression model of the relationship between VA and transplant status (table 22).

In the event of a transplant failing, the transplant failure regression coefficients are applied in the base case. An alternative value of baseline results may be applied instead.

The VA probability distributions are represented by table 23 to table 25. In terms of uncertainty a Normal probability distribution is applied to each estimated parameter in the regression model with a mean of the estimate and the standard error as stated in table 22. PSA samples new estimates from these distributions which are then translated into new VA state probabilities.

The success of transplantation and lack of stromal scarring are also used to drive the probability of pain/burning/photophobia and whether there is disfigurement.

In both models, utility is driven by the combination of VA in both the BSE and WSE. The specific utility value assigned to any combination is a function of the underlying BSE based utility mappings applied to an algorithm which splits the mapping from a single VA measurement to a BSE/WSE combination to utility mapping. Our base case model selects the Czoski-Murray et al(120) group means original mapping as it has an established use in NICE HTA algorithms and applies a weighting estimated from Finger et al(111) data. The weighting values, termed the BSE/WSE model are shown in table 41 and the full BSE/WSE combination to utility mapping table is shown in table 42.

There is no probabilistic distribution assigned to this element, although both models allow selection of different underlying BSE mappings and BSE/WSE weightings including the values estimated from the bespoke general population SG study.

An additional utility decrement can occur if there is moderate or severe pain/burning/photophobia. These secondary conditions are modelled together as there was a high degree of correlation between them in the HLSTM01 dataset. The base case value attached to the presence of moderate or severe pain/burning/ photophobia is derived from the EQ-5D 3L tariff and uses the level 2 and 3 decrements of -0.123 and -0.386 respectively. Alternative values of no decrement and that derived from the general population SG method of -0.291 for both moderate and severe may be used.

A final utility decrement can occur due to disfigurement which as defined as the presence of either/or corneal opacity, superficial corneal neovascularisation and inflammation. In practice this is measures as an eye with an unsuccessful transplant or the presence of stromal scarring. If there is disfigurement in any eye, then the base case utility decrement from the general population SG is used and a value of -0.318 is used. As with pain, an alternative of zero utility decrement can be selected.

## *5.7 Base-case results*

### Base-case incremental cost effectiveness analysis results

**Table 51: Base-case results – Unilateral LSCD**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 22,158 | 12.64 | | | Dominates | Dominates | |
| Ir-CLAL | £ 77,434 | 9.73 | £ 27,313 | -2.92 | Dominates | | |
| KLAL | £ 89,256 | 9.80 | £ 3,256 | 0.07 | Dominates | | |
| HOLOCLAR | £ [redacted] | 12.09 | £ [redacted] | 2.29 | Dominates | | £ 7,185 |
| BSC | £ 101,535 | 7.18 | 18610.3759 | -4.91 | | | |

**Table 52: Base-case results – Bilateral LSCD**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 47,402 | 10.08 | | | Dominates | Dominates | |
| Ir-CLAL | £ 155,430 | 6.36 | £ 108,029 | -3.72 | Dominates | | |
| KLAL | £ 173,844 | 6.56 | £ 18,414 | 0.20 | Dominates | | |
| HOLOCLAR | £ [redacted] | 9.25 | £ [redacted] | 2.69 | Dominates | | £ 12,438 |
| BSC | £ 193,323 | 2.44 | £ 1,906 | -6.81 | | | |

The base case results suggest that all treatment options dominate BSC. The results are partly driven by the low HRQoL that LSCD patients with severely limited VA in at least one eye incur especially when combined with utility decrements for pain and disfigurement. Even a few years respite adds Quality of Life. There is also a high cost to unresolved LSCD which is managed by BSC – expert opinion suggests that frequent flare-ups of pain and inflammation which need to be treated by expensive autologous serum eye-drops quickly increase costs. Costs increase to the extent that they offset the product cost of HOLOCLAR over a life-time perspective given the relatively young age of the prevalent population.

With the highest success rates (at least from the pooled literature review), an assumption that the one-year success rate persists over time and no product costs, means that CLAU is the most cost-effective option. This result is robust to sensitivity analysis.

The result that Lr-CLAL and KLAL are less cost-effective than HOLOCLAR is driven by the failure rates over time of the allografts as shown in table 53.

Immunosuppression costs and adverse events related to them have little impact but a return to BSC over time for many eyes leads to offset costs and QALY loses that make HOLOCLAR cost-effective relative to these options.

The tables also show the results with CLAU excluded. This is particularly pertinent for the bilateral case where the literature do not support the use of CLAU in bilateral cases. Without CLAU it can be seen that HOLOCLAR dominates in the unilateral case and has a lower ICER, well within the threshold values, in the bilateral case.

**Table 53: Markov trace over time**

| Treatment | Model State | Year 5 | Year 10 | Year 20 | Year 30 | Year 40 |
|---|---|---|---|---|---|---|
| HOLOCLAR | Stable | 76% | 74% | 67% | 53% | 25% |
| | BSC | 23% | 22% | 20% | 16% | 8% |
| | Dead | 2% | 4% | 12% | 32% | 67% |
| CLAU | Stable | 85% | 83% | 76% | 59% | 28% |
| | BSC | 13% | 13% | 12% | 9% | 4% |
| | Dead | 2% | 4% | 12% | 32% | 67% |
| lr-CLAL | Stable | 60% | 38% | 14% | 5% | 1% |
| | BSC | 38% | 58% | 73% | 63% | 32% |
| | Dead | 2% | 4% | 12% | 32% | 67% |

| | | | | | | |
|---|---|---|---|---|---|---|
| KLAL | Stable | 78% | 57% | 13% | 2% | 0% |
| | BSC | 20% | 39% | 74% | 67% | 33% |
| | Dead | 2% | 4% | 12% | 32% | 67% |

**Disaggregated results of the base case incremental cost effectiveness analysis**

Table 54 and table 55 show the overall contributions to utility in the unilateral and bilateral cases from the three sources: VA, pain/burning/photophobia and disfigurement.

**Table 54: Utility gains by source – Unilateral LSCD**

| | VA Utility | Loss due to pain | Loss due to disfigurement | QALY gain relative to BSC from VA | QALY gain relative to BSC from Pain | QALY gain relative to BSC from Disfigurement |
|---|---|---|---|---|---|---|
| BSC | 16.27 | -0.48 | -8.60 | | | |
| Lr-CLAL | 17.13 | -0.16 | -7.26 | 0.87 | 0.32 | 1.35 |
| KLAL | 17.16 | -0.15 | -7.22 | 0.90 | 0.33 | 1.38 |
| HOLOCLAR | 17.57 | -0.10 | -5.38 | 1.30 | 0.38 | 3.23 |
| CLAU | 17.67 | -0.09 | -4.94 | 1.40 | 0.39 | 3.67 |

**Table 55: Utility gains by source - Bilateral LSCD**

| | VA Utility | Loss due to pain | Loss due to disfigurement | QALY gain relative to BSC from VA | QALY gain relative to BSC from Pain | QALY gain relative to BSC from Disfigurement |
|---|---|---|---|---|---|---|
| BSC | 11.52 | -0.48 | -9.08 | | | |
| Lr-CLAL | 13.78 | -0.16 | -7.43 | 2.26 | 0.32 | 1.65 |
| KLAL | 14.11 | -0.15 | -7.55 | 2.58 | 0.32 | 1.53 |
| HOLOCLAR | 14.86 | -0.10 | -5.61 | 3.34 | 0.37 | 3.47 |
| CLAU | 15.17 | -0.09 | -5.10 | 3.65 | 0.39 | 3.99 |

In both cases although total utility is mainly driven by the BSE/WSE utility, it is the utility decrement associated with disfigurement which generates the largest incremental differences between treatments. The utility decrement associated with pain/burning/photophobia has little impact due to the small prevalence within the patient population.

The relative utility increments due to disfigurement in the bilateral case are smaller than in the unilateral case due to the assumption that both eyes must be free of disfigurement to avoid the utility decrement.

**Table 56: Cost generation by transplant costs and BSC costs - Unilateral model**

| | Total Costs | Transplant Costs | BSC costs |
|---|---|---|---|
| CLAU | £ 22,158 | £ 5,329 | £ 16,829 |
| Lr-CLAL | £ 77,434 | £ 6,368 | £ 71,067 |
| KLAL | £ 89,256 | £ 17,292 | £ 71,964 |
| HOLOCLAR | £ [redacted] | £ [redacted] | £ 24,161 |
| BSC | £ 101,535 | £ - | £ 101,535 |

**Table 57: Cost generation by transplant costs and BSC costs - Bilateral model**

| | Total Costs | Transplant Costs | BSC costs |
|---|---|---|---|
| CLAU | £ 47,402 | £ 10,559 | £ 36,843 |
| Lr-CLAL | £ 155,430 | £ 12,626 | £ 142,804 |
| KLAL | £ 173,844 | £ 33,066 | £ 140,778 |
| HOLOCLAR | £ [redacted] | £ [redacted] | £ 54,576 |
| BSC | £ 193,323 | £ - | £ 193,323 |

Table 56 and Table 57 show the breakdown of total costs of each treatment option by those generated by transplantation including hospital procedures, product costs, medication and monitoring, etc. and those created by treatment of LSCD in BSC – primarily the use of autologous serum eye drops.

The highest transplant costs are associated with HOLOCLAR and driven by the product cost itself. The product costs and possibility of doing re-transplantation raises the costs of HOLOCLAR and KLAL higher than CLAU and lr-CLAL.

The costs of BSC in the unilateral case are estimated at £3,758 per annum, of which 88% is generated by the use of autologous serum eye drops.

## *5.8 Sensitivity analyses*

The sensitivity analysis models discussed below are presented in Appendix 8.

**Probabilistic sensitivity analysis**

PSA using listed distributions around regression model results and literature transplant success over time values yield CEACs which suggest 100% likelihood of CLAU being the most cost-effective option.

### Deterministic sensitivity analysis

The excel model permits many variations of parameter assumptions. We report some variations to the base case model here which vary: discount rate; exclusion of pain and disfigurement utility decrements; application of different rates of success over time for CLAU, lr-CLAL and KLAL and differing model time perspectives.

**Table 58: Unilateral LSCD as per base case but 3.5% discount rates**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 18,651 | 9.34 | | | Dominates | Dominates | |
| lr-CLAL | £ 55,782 | 7.41 | £ 37,131 | -1.94 | Dominates | | |
| KLAL | £ 65,932 | 7.48 | £ 10,150 | 0.07 | Dominates | | |
| BSC | £ 75,289 | 5.33 | £ 9,357 | -2.15 | | | |
| HOLOCLAR | £ [redacted] | 8.93 | £ [redacted] | 3.61 | £ 5,159 | | £ 21,182 |

**Table 59: Bilateral LSCD as per base case but 3.5% discount rates**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 40,223 | 7.38 | | | Dominates | Dominates | |
| lr-CLAL | £ 112,364 | 4.93 | £ 72,141 | -2.46 | Dominates | | |
| KLAL | £ 127,407 | 5.12 | £ 15,044 | 0.20 | Dominates | | |
| BSC | £ 143,350 | 1.81 | £ 15,943 | -3.31 | | | |
| HOLOCLAR | £ [redacted] | 6.77 | £ [redacted] | 4.96 | £ 6,708 | | £ 34,817 |

**Table 60: Unilateral LSCD as per base case but no disfigurement utility decrement**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 22,158 | 17.58 | | | Dominates | Dominates | |
| lr-CLAL | £ 77,434 | 16.98 | £ 55,276 | -0.60 | Dominates | | |
| KLAL | £ 89,256 | 17.02 | £ 11,821 | 0.04 | Dominates | | |
| HOLOCLAR | £ [redacted] | 17.47 | £ [redacted] | 0.45 | Dominates | | £ 35,076 |
| BSC | £ 101,535 | 15.79 | £ 7,112 | -1.68 | | | |

**Table 61: Bilateral LSCD as per base case but no disfigurement utility decrement**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 47,402 | 15.08 | | | Dominates | Dominates | |
| Ir-CLAL | £ 155,430 | 13.63 | £ 108,029 | -1.46 | Dominates | | |
| KLAL | £ 173,844 | 13.95 | £ 18,414 | 0.33 | Dominates | | |
| HOLOCLAR | £ [redacted] | 14.76 | £ [redacted] | 0.80 | Dominates | | £ 31,850 |
| BSC | £ 193,323 | 11.05 | £ 1,906 | -3.71 | | | |

**Table 62: Unilateral LSCD as per base case but 3.5% discount rate, no disfigurement utility decrement and 4 flare-ups in BSC p.a.**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 27,401 | 13.04 | | | Dominates | Dominates | |
| Ir-CLAL | £ 95,977 | 12.64 | £ 68,576 | -0.40 | Dominates | | |
| KLAL | £ 101,717 | 12.67 | £ 5,739 | 0.03 | Dominates | | |
| HOLOCLAR | £ [redacted] | 12.95 | £ [redacted] | 0.28 | Dominates | | £ 25,164 |
| BSC | £ 141,540 | 11.71 | £ 37,711 | -1.24 | | | |

**Table 63: Bilateral LSCD as per base case but 3.5% discount rate, no disfigurement utility decrement and 4 flare-ups in BSC p.a.**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 60,593 | 11.14 | | | Dominates | Dominates | |
| Ir-CLAL | £ 193,779 | 10.18 | £ 133,186 | -0.96 | Dominates | | |
| KLAL | £ 196,845 | 10.50 | £ 3,066 | 0.32 | Dominates | | £ 9,660 |
| HOLOCLAR | £ [redacted] | 10.90 | £ [redacted] | 0.40 | Dominates | | £ 39,595 |
| BSC | £ 275,853 | 8.19 | £ 63,100 | -2.71 | | | |

**Table 64: Unilateral LSCD as per base case but no disfigurement decrement and CLAU = Burcu**(35) **rates, Ir-CLAL = Gomes**(47) **rates and KLAL = Solomon**(102) **rates**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 41,298 | 17.36 | | | Dominates | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| KLAL | £ 90,292 | 17.02 | £ 48,994 | -0.34 | Dominates | | |
| Ir-CLAL | £ 94,094 | 16.79 | £ 3,803 | -0.22 | Dominates | | |
| HOLOCLAR | £ [redacted] | 17.47 | £ [redacted] | 0.67 | Dominates | £ 488,615 | £ 9,138 |
| BSC | £ 101,535 | 15.79 | £ 7,112 | -1.68 | | | |

**Table 65: Bilateral LSCD as per base case but no disfigurement decrement and CLAU = Burcu**(35) **rates, Ir-CLAL = Gomes**(47) **rates and KLAL = Solomon**(102) **rates**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 84,951 | 14.54 | | | Dominates | | |
| KLAL | £ 175,888 | 13.94 | £ 90,937 | -0.60 | Dominates | | |
| Ir-CLAL | £ 188,336 | 13.16 | £ 12,448 | -0.78 | Dominates | | |
| HOLOCLAR | £ [redacted] | 14.76 | £ [redacted] | 1.60 | Dominates | £ 485,692 | £ 19,085 |
| BSC | £ 193,323 | 11.05 | £ 1,906 | -3.71 | | | |

**Table 66: Unilateral LSCD as per base case CLAU = Burcu**(35) **rates, Ir-CLAL = Gomes**(47) **rates and KLAL = Solomon**(102) **rates and 22 year time horizon**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 30,085 | 7.72 | | | Dominates | | |
| KLAL | £ 57,398 | 7.06 | £ 27,313 | -0.66 | Dominates | | |
| Ir-CLAL | £ 60,654 | 6.15 | £ 3,256 | -0.91 | Dominates | | |
| BSC | £ 68,012 | 4.81 | £ 7,358 | -1.34 | | | |
| HOLOCLAR | £ [redacted] | 8.06 | £ [redacted] | 3.25 | £ 5,733 | £ 167,223 | £ 29,369 |

**Table 67: Bilateral LSCD as per base case but 1.5% discount rates and CLAU = Burcu**(35) **rates, Ir-CLAL = Gomes**(47) **rates and KLAL = Solomon**(102) **rates and 28 year time horizon**

| | Costs | QALYs | Inc Costs | Inc QALYs | ICER versus Baseline | ICER | ICER w/o CLAU |
|---|---|---|---|---|---|---|---|
| CLAU | £ 71,202 | 6.87 | | | Dominates | | |
| KLAL | £ 135,035 | 5.65 | £ 63,833 | -1.22 | Dominates | | |
| Ir-CLAL | £ 147,146 | 4.31 | £ 12,110 | -1.34 | Dominates | | |
| BSC | £ 154,056 | 1.95 | £ 6,910 | -2.36 | | | |
| HOLOCLAR | £ [redacted] | 7.30 | £ [redacted] | 5.36 | £ 5,060 | £ 255,563 | £ 27,898 |

**Summary of sensitivity analyses results**

Despite the multiple combinations of alternatives the results remain reasonably robust. In all circumstances CLAU is the cost-effective option and only when we use the rates of success seen by Burcu(35) is it not the dominant option. However, if CLAU is excluded from the choice set HOLOCLAR frequently becomes the most cost-effective option. These results are most sensitive to changes in discount rate and whether disfigurement decrements are used.

## *5.9 Subgroup analysis*

A number of subgroup analyses were undertaken but did not lead to any substantive changes to the results and so are not reported.

For example: initial treatment of BSE or WSE for the bilateral model; female patient; restricting analyses to good, average or poor underlying VA eyes only all had no major impact on results that change conclusions or lead to additional insight.

## *5.10 Validation*

**Validation of de novo cost-effectiveness analysis**

Predicted distributions of VA states and presence of stromal scarring and pain/burning/photophobia were matched to observed values in the HLSTM01 dataset and showed a close match that was maintained over time (Table 26, Table 31 and Table 35)

Lack of any published data on costs or QALYs of LSCD make external validation difficult. However the use of BSE to utility mapping algorithms is extensively used, including in recent NICE evaluations.

Utility decrements to pain are based on established EQ-5D tariffs.

The impact of disfigurement on utility maybe the biggest issue. The YHEC SG exercise estimates a large utility decrement to which ICER estimates are sensitive if omitted. However expert opinion informs us that patients often appear to rate appearance of the eye greater than VA.

With limited options to benchmark model results against external data our approach has been to subject the model to a wide range of sensitivity analyses, which have provided generally consistent results.

## *5.11 Interpretation and conclusions of economic evidence*

The main drivers of the economic argument are as follows.

Chronic LSCD secondary to chemical or physical burns primarily occurs in a young population and without transplant will remain unresolved over a long period of time.

The visual acuity of affected eyes is typically very low – in the range of light perception to counting fingers. Evidence suggests very low VA in a WSE even with a good VA in a BSE has some utility decrement. This may be combined with a decrement for pain and, as suggested by experts and verified in a general population SG, a decrement due to disfigurement. These utility decrements persist over time.

Coupled with a loss of HRQoL, there are expected high costs, primarily these are associated with the cost of providing courses of autologous eye serum drops to treat flare-ups of ocular symptoms associated with LSCD. Expert opinion suggests these costs can be as high as £7,000 per annum (57), though our base case model adopts a far more conservative figure under £4,000 p.a.

With a high and long term burden of illness there is considerable scope for a curative treatment to be cost effective, even one which has high upfront costs.

According to the HLSTM01 trial,(7) successful transplantation of LSCD cells and a re-establishment of a stable ocular surface followed by removal of stromal scarring if necessary can restore an improved VA in the WSE, a lack of pain/burning/photophobia and improved cosmetic appearance that, at least in the case of HOLOCLAR, persists over time. We assume that the same long-term (post one year) rates apply to CLAU but not lr-CLAL and KLAL which are known to have high rejection rates over time.

As such, given reasonably high success rates ranging from 67% to 100%, CLAU looks to be the most cost-effective treatment for LSCD. However given the relatively large prevalent to incident population it is clear that CLAU may not always be a

viable option or is one that has potentially failed in the past. Furthermore, where CLAU is not appropriate HOLOCLAR becomes the most cost-effective option – a function of its own high success rate, the proven resilience over time and the ability to retreat if the first or second transplant fails.

Furthermore, none of the surveyed literature suggested any role for CLAU in treating bilateral LSCD and lr-CLAL, KLAL and BSC may be the plausible alternatives to HOLOCLAR. In which case HOLOCLAR is cost-effective over a large range of scenarios.

The economic modeling of LSCD is hindered by gaps in the evidence base. The main issues of concern are:

1. The Health Related Quality of Life associated with unilateral and bilateral LSCD. There are no generic or disease specific measures which have collected information from this group of patients and it is uncertain to what extent VA from WSE, pain/burning/photophobia and disfigurement may impact on utility. The impact of disfigurement appears to be the parameter to which results are most sensitive.

2. There are no RCTs comparing treatments to gage relative effectiveness in the short- or long-run, instead there are a small number of small volume case-studies which permit little in the way of adjusting for heterogeneous populations.

3. There is little published evidence on the costs of LSCD in BSC

Nevertheless the limited published evidence combined with some expert opinion provide results which are robust to many of the uncertain elements.

# 6 Assessment of factors relevant to the NHS and other parties

A budget impact model has been constructed on the basis of the following data. Table 68 shows the estimated prevalent and incidence populations based on available literature, expert opinion and market research.(3,57,69,70) The patient numbers identified are relatively small scale. Of note is the high rate of bilateral cases in the prevalent population relative to the incidence population.

**Table 68: BIM Parameters**

| | | | |
|---|---|---|---|
| **Prevalence** | 121 patients will be the maximum estimated prevalent population for Holoclar | 121 | EPAR<br>ONS Data<br>Chiesi market research |
| **Incidence** | In addition to the prevalent population, the estimated incidence of new cases of severe chemical corneal injury in the UK is 0.02 in 100,000 people i.e. 13 new cases per year. | 13 | MacDonald 2009 (36) |
| **What percentage of your patients with LSCD have the condition in one eye vs. in both eyes?** | 30% Unilateral, 70% Bilateral. **Prevalent cases.**<br>90% Unilateral, 10% Bilateral. **Incident cases.** | | Expert Opinion(56) |
| **Base Case** | Two thirds of UK Surgical Ophthalmology centres have advised Chiesi the current pool of eligible patients that they are aware of is approximately 51 patients, representing both the pool & incidence of eligible patients in 2015. | 51 | Chiesi Ltd<br>Data on file(122) |
| **List Price** | Holoclar patient access scheme price (ex VAT) per treatment per eye: | [redacted] | |

Market research suggests 121 prevalent patients (3,69,70) with 13 new cases per year.(36) Of 121 prevalent patients, expert opinion estimates that 70% have bilateral LSCD (85 patients and therefore 170 eyes) and 30% have unilateral LSCD. An estimated number of 13 new cases are expected to be generated per year of which 90% have unilateral LSCD and 10% have bilateral LSCD, i.e. 12 patients/1eye and 1patient/2 eyes.

For prevalent cases and given the duration of unresolved LSCD of patients in HLSTM01(7), one plausible assumption is that all of these patients may have exhausted alternative treatment options. In such a case the HOLOCLAR market share of these patients is limited to the proportion of patients who may be eligible for HOLOCLAR. The UK surgical ophthalmology centre estimate an approximate proportion of 40% of patients for which HOLOCLAR may be a suitable option.(122)

For new cases, the current market share for the alternative treatments is unclear, though given the dominance in the heath economic argument CLAU is expected to be first line for unilateral. However current treatment guidelines do not recommend CLAU for treatment of bilateral LSCD. Based on the sample sizes of the pooled evidence for lr-CLAL and KLAL we assume a 15:85 split between allograft options.

Table 69 shows the expected costs as used in the base case economic model. Transplant costs include biopsy procedure costs, main transplant costs, product costs, medications and post-op follow-up care. Table 49 shows the unit costs and their sources, which are generally derived from Reference Costs or MIMs. For Holoclar, the unit cost used in the base case is the patient access scheme (simple discount scheme) price referred to PASLU for inclusion in this submission.

For eyes that achieve a stable ocular surface but still have stromal scarring, a keratoplasty may be required. Surgery plus follow-up care is estimated at £3,991.

BSC of unresolved LSCD per eye is costed at £3,785 per annum.

**Table 69: Year one and onwards costs as used in economic model**

| Operation | Single Transplant Costs |
|---|---|
| CLAU | £ 6,221 |
| Lr-CLAL | £ 8,185 |
| Holoclar | [redacted] |
| KLAL | £ 9,215 |
| Keratoplasty | £ 3,991 |

Table 50 shows the relevant probabilities of transplant success, transplant survival over time, re-operation and probability of keratoplasty.

Table 70 shows the expected costs over a five year time period given the option of treatment with Holoclar relative to BSC. We assume treatment of 24 eyes per year. With a 68% success rate this leads to an estimate of 16 successful transplants, of which approximately 8 will go on to have a further keratoplasty. These 16 successfully treated eyes will have each offset BSC costs of £3,785 per annum which will accumulate over time. Thus in year 2 the total offset costs will represent the new offset costs of the year 2 eye treatments plus the continued offset costs of the 16 successful transplants of the year before.

**Table 70: BIM of Holoclar against BSC over a 5 year period**

| Year | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Transplants | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Success | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Transplant cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| keratoplasty cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BSC costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Offset BSC costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The net cost to the NHS falls over time as the impact of offset costs of successfully treated accumulates. By year 5 there are expected to be 82 eyes no longer generating BSC costs and thus creating a saving in the NHS of [redacted] which partially offsets the approximately [redacted] of costs of transplants. The offset costs will further accumulate over time whilst the prevalent population size is expected to fall. At a rate of treatment of 24 eyes per year the existing prevalent population that are eligible for Holoclar (assumed 40%) and thus generate costs may be exhausted by year 5. Thus from year 5 onwards there may be a net benefit to the NHS of approximately £310k per annum which will decrease as those patients die.

For the incident population case of 12 unilateral cases the underlying assumption is that CLAU will remain the first treatment of choice. However expert opinion has estimated up to 30% of patients may refuse or not be eligible for CLAU.(122) In these cases, plus the bilateral case both Ir-CLAL and KLAL become alternatives. The number of potential treatments will be small, estimated at a potential 6 eyes per annum. Table 71 shows the relevant figures if all 6 potential eyes are treated.

**Table 71: BI for incident cases all treated with Holoclar**

| Year | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Transplant cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| keratoplasty cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BSC costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Offset BSC costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

A similar calculation may be constructed for KLAL and Ir-CLAL shown in table 72 and table 73.

**Table 72: BI for KLAL versus BSC for incident cases**

| Year | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Transplant cost | £ 52,903 | £ 52,903 | £ 52,903 | £ 52,903 | £ 52,903 |
| keratoplasty cost | £ 10,939 | £ 10,939 | £ 10,939 | £ 10,939 | £ 10,939 |
| BSC costs | £ 1,363 | £ 7,635 | £ 17,688 | £ 30,652 | £ 45,858 |
| Offset BSC costs | -£ 21,347 | -£ 37,785 | -£ 50,442 | -£ 60,188 | -£ 67,692 |
| | | | | | |
| Total | £ 43,863 | £ 33,704 | £ 31,106 | £ 34,331 | £ 42,038 |

**Table 73: BI for Ir-CLAL versus BSC for incidence cases**

| Year | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Transplant cost | £ 50,933 | £ 50,933 | £ 50,933 | £ 50,933 | £ 50,933 |
| keratoplasty cost | £ 11,055 | £ 11,055 | £ 11,055 | £ 11,055 | £ 11,055 |
| BSC costs | £ 1,136 | £ 3,997 | £ 8,446 | £ 14,356 | £ 21,611 |
| Offset BSC costs | -£ 21,575 | -£ 41,423 | -£ 59,684 | -£ 76,484 | -£ 91,939 |
| | | | | | |
| Total | £ 41,556 | £ 24,574 | £ 10,769 | -£ 114 | -£ 8,310 |

The net impact on the NHS budget will depend on the rate of substitution between alternatives. For example if all 6 eyes are switched from potentially KLAL or Ir-CLAL because of the longer term benefits of Holoclar (and there is an 85:15 ratio) between KLAL and Ir-CLAL. Then the net impact on costs will be: [redacted] over 5 years.

In total if Holoclar is used to treat all of the prevalent population for which it is applicable and all of the incidence cases which are not eligible for CLAU, the net impact on NHS expenditure over 5 years would be: [redacted].

Even though these numbers do not reflect the longer term cost savings of Holoclar they show a very modest budget impact in the short-run. This is not surprising as the number of LSCD patients is known to be very low.

The calculation is based on the economic modelling costs and are a function of the estimated success and survival rates over time, which we know are uncertain as they are derived from a small non-randomised evidence base. There is also little data on the market share of each type of transplant. Nevertheless, with such small numbers involved, the budget impact is minimal to the NHS in England.

# 7 References


1. European Medicines Agency. First stem-cell therapy recommended for approval in EU; 19th December 2014 [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/12/news_detail_002239.jsp&mid=WC0b01ac058004d5c1 (accessed January 2017).
2. Shortt AJ, Tuft SJ, Daniels JT. Corneal stem cells in the eye clinic. Br Med Bull. 2011;100(1):209–25.
3. European Medicines Agency. Assessment Report Holoclar. [Internet]. 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/002450/WC500183405.pdf (accessed January 2017).
4. European Medicines Agency. 1995-2015 Working together for safe and effective medicines. [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp&mid=WC0b01ac058087addd (accessedJanuary 2017).
5. The Ministry of Defence. The Armed Forces Covenant [Internet]. The Ministry of Defence. 2011. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/49469/the_armed_forces_covenant.pdf (accessed January 2017).
6. Chiesi Farmaceutici S.p.A. Holoclar 79,000 - 316,000 cells/cm2 living tissue equivalent. Summary of Product Characteristics, December 2015.
7. Chiesi Farmaceutici S.p.A. Study report: CCD-0917-CSR-0037. Retrospective evaluation of the efficacy and safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with LSCD due to ocular burns (HLSTM01), 15th February 2015.
8. Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, Pellegrini G. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010;363(2):147–55.
9. Cauchi PA, Ang GS, Azuara-Blanco A, Burr JM. A Systematic Literature Review of Surgical Interventions for Limbal Stem Cell Deficiency in Humans. Am J Ophthalmol. 2008;146(2).
10. Dua HS, Miri A, Said DG. Contemporary limbal stem cell transplantation - a review. Clin Experiment Ophthalmol. 2010;38(2):104–17.
11. Atallah M, Palioura S, Perez V, Amescua G. Limbal stem cell transplantation: current perspectives. Clin Ophthalmol. 2016;10:593–602.
12. Chiesi Farmaceutici S.p.A. Protocol Outline: Multinational, multicentre, prospective, open label, uncontrolled clinical trial to assess the efficacy & safety of ACLSCT for restoration of corneal epithelium in patients with LSCD due to ocular burns (HOLOCORE), 25th May 2015.
13. Chiesi Farmaceutici S.p.A. Multinational, Multicentre, Prospective, Long-Term Safety and Efficacy Follow-Up Study After Autologous Cultivated Limbal Stem Cells Transplantation (ACLSCT) for Restoration of Corneal Epithelium In Patients LSCD Due to Ocular Burns (HOLOCORE-FU). 2015.
14. Chiesi Farmaceutici S.p.A. Protocol outline: Long-term safety after Holoclar® implant for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns: observational study of routine clinical practice (HOLOSIGHT), 15th June 2015.
15. Department of Health. Letter from Kathy Crawford. November 2016.

16. Haymarket Media Group Ltd. MIMS Online. August 2016.
17. NHS England. MEDICINES NOT REIMBURSED THROUGH NATIONAL PRICES AND DIRECTLY COMMISSIONED BY NHS ENGLAND. Version 10.0 Published April 2016. [Internet]. 2016. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2014/06/nhse-drugs-list-v10.pdf (accessed January 2017).
18. ValueBase HealthCare Limited. Novartis, Astellas and Chiesi Win Prix Galien Prizes on Night of Firsts for UK Pharma. [Internet]. 2016. Available from: http://prixgalien.co.uk/docs/Press_Release_Winners.pdf (accessed January 2017).
19. Crabb N. Valuing treatments – the regenerative medicine challenge. [Internet]. 2015. Available from: https://www.nice.org.uk/news/blog/valuing-treatments-the-regenerative-medicine-challenge (accessed January 2017).
20. Claxton K, Longo R, Longworth L, McCabe C, Wailoo A. The Value of Innovation: Report by the Decision Support Unit. [Internet]. 2009. Available from: http://www.nicedsu.org.uk/Value-of-Innovation(2474847).htm (accessed January 2017).
21. Dillon A. Carrying NICE over the threshold. [Internet]. 2015. Available from: https://www.nice.org.uk/news/blog/carrying-nice-over-the-threshold (accessed January 2017).
22. Jenkins C, Tuft S, Liu C, Buckley R. Limbal Transplantation in the Manage Ment of Chronic Contact-Lens- Associated Epitheliopathy. 1993;7:629–33.
23. Dua H, Joseph A, Shanmuganathan V, Jones R. Stem cell differentiation and the effects of deficiency. Eye (Lond). 2003;17(8):877–85.
24. Sejpal K, Bakhtiari P, Deng SX. Presentation, diagnosis and management of limbal stem cell deficiency. Middle East Afr J Ophthalmol. 2013;20(1):5–10.
25. Haagdorens M, Van Acker SI, Van Gerwen V, N?? Dhubhghaill S, Koppen C, Tassignon MJ, et al. Limbal stem cell deficiency: Current treatment options and emerging therapies. Stem Cells Int vol 2016, Artic ID 9798374, 22 pages, 2016 doi101155/2016/9798374.
26. Dua HS, Saini JS, Azuara-Blanco A, Gupta P. Limbal stem cell deficiency: concept, aetiology, clinical presentation, diagnosis and management. Indian J Ophthalmol. 2000;48(2):83–92.
27. Osei-Bempong C, Figueiredo FC, Lako M. The limbal epithelium of the eye- A review of limbal stem cell biology, disease and treatment. Bioessays [Internet]. 2013;35(3):211–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23129317 (accessed January 2017).
28. Hatch K, Dana R. The structure and function of the limbal stem cell and the disease states associated with limbal stem cell deficiency. Int Ophthalmol Clin. 2009;149(1):43–52.
29. Espana EM, Grueterich M, Romano AC, Touhami A, Tseng SC. Idiopathic limbal stem cell deficiency. Ophthalmology. 2002;109(11):2004–10.
30. Al-Swailem SA. Graft failure: II. Ocular surface complications. Int Ophthalmol. 2008;28(3):175–89.
31. Lagali N, Edén U, Utheim TP, Chen X, Riise R, Dellby A et al. In vivo morphology of the limbal palisades of vogt correlates with progressive stem cell deficiency in aniridia-related keratopathy. Invest Ophthalmol Vis Sci. 2013;54(8):5333–42.
32. Lichtinger A, Pe'er J, Frucht-Pery J, Solomon A. Limbal Stem Cell Deficiency

after Topical Mitomycin C Therapy for Primary Acquired Melanosis with Atypia. Ophthalmology. 2010;117(3):431–7.
33. Shaharuddin B, Ahmad S, Ali S, Meeson A. Limbal side population cells: a future treatment for limbal stem cell deficiency. Regen Med. 2013;8(3):319–31.
34. Crawford AZ, Mcghee CNJ. Management of limbal stem cell deficiency in severe ocular chemical burns. Clin Exp Ophthalmol. 2012;40(3):227–9.
35. Burcu A, Yalniz-Akkaya Z, Ozdemir MF, Erdem E, Onat MM, Ornek F. Surgical rehabilitation following ocular chemical injury. Cutan Ocul Toxicol. 2014;33(1):42–8.
36. Macdonald EC a, Cauchi P a, Azuara-Blanco A, Foot B. Surveillance of severe chemical corneal injuries in the UK. Br J Ophthalmol. 2009;93(9):1177–80.
37. Baylis O, Figueiredo F, Henein C, Lako M, Ahmad S. 13 Years of cultured limbal epithelial cell therapy: A review of the outcomes. J Cell Biochem. 2011;112(4):993–1002.
38. Bobba S, Chow S, Watson S, Di Girolamo N. Clinical outcomes of xeno-free expansion and transplantation of autologous ocular surface epithelial stem cells via contact lens delivery: a prospective case series. Stem Cell Res Ther. 2015;6:23.
39. Graham JS, Schoneboom BA. Historical perspective on effects and treatment of sulfur mustard injuries. Chem Biol Interact. 2013;206(3):512–22.
40. Medical Advisory Secretariat. Limbal stem cell transplantation: an evidence-based analysis. Ontario Health Technology Assessment Series. [Internet]. Vol. 8. 2008. Available from: www.health.gov.on.ca/ohtas (accessed January 2017).
41. Fish R, Davidson RS. Management of ocular thermal and chemical injuries, including amniotic membrane therapy. Curr Opin Ophthalmol. 2010;21(4):317–21.
42. Titiyal JS, Sharma N, Agarwal AK, Prakash G, Tandon R, Vajpayee R. Live Related versus Cadaveric Limbal Allograft in Limbal Stem Cell Deficiency. Ocul Immunol Inflamm. 2015;23(3):232–9.
43. Shortt AJ, Secker GA, Notara MD, Limb GA, Khaw PT, Tuft SJ, et al. Transplantation of Ex Vivo Cultured Limbal Epithelial Stem Cells: A Review of Techniques and Clinical Results. Surv Ophthalmol. 2007;52(5):483–502.
44. Ramachandran C, Basu S, Sangwan V, Balasubramanian D. Concise Review: The Coming of Age of Stem Cell Treatment for Corneal Surface Damage. Stem Cells Tranlsational Med. 2014;3:1160–8.
45. Shortt AJ, Secker GA, Rajan MS, Meligonis G, Dart JK, Tuft SJ, et al. Ex Vivo Expansion and Transplantation of Limbal Epithelial Stem Cells. Ophthalmology. 2008;115(11):1989–97.
46. Miri A, Al-Deiri B, Dua HS. Long-term Outcomes of Autolimbal and Allolimbal Transplants. Ophthalmology. 2010;117(6):1207–13.
47. Gomes JA, dos Santos MS, Cunha MC, Mascaro VL, Barros Jde N, de Sousa LB. Amniotic membrane transplantation for partial and total limbal stem cell deficiency secondary to chemical burn. Ophthalmology [Internet]. 2003;110(3):466–73. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12623806 (accessed January 2017).
48. Ucakhan OO, Koklu G, Firat E. Nonpreserved human amniotic membrane transplantation in acute and chronic chemical eye injuries. Cornea. 2002;21(2):169–72.

49. Dua HS A-BA. Allo-limbal transplantation in patients with limbal stem cell deficiency. Br J Ophthalmol. 1999;83(4):414–9.
50. Eberwein P, Böhringer D, Schwartzkopff J, Birnbaum F, Reinhard T. Allogenic limbo-keratoplasty with conjunctivoplasty, mitomycin C, and amniotic membrane for bilateral limbal stem cell deficiency. Ophthalmology. 2012;119(5):930–7.
51. Reinhard T, Spelsberg H, Henke L, Kontopoulos T, Enczmann J, Wernet P, et al. Long-term results of allogeneic penetrating limbo-keratoplasty in total limbal stem cell deficiency. Ophthalmology. 2004;111(4):775–82.
52. Jonsdotttir E, Stevenevi U. orneal grafts including limbal stem cells in selected patients with stem cell deficiency. Acta Opthalmologica. 2014;2014.
53. Baradaran-Rafii A, Ebrahimi M, Kanavi MR, Taghi-Abadi E, Aghdami N, Eslani M, et al. Midterm outcomes of autologous cultivated limbal stem cell transplantation with or without penetrating keratoplasty. Cornea. 2010;29(5):502–9.
54. Baradaran-Rafii A, Eslani M, Jamali H, Karimian F, Tailor UA, Djalilian AR. Postoperative complications of conjunctival limbal autograft surgery. Cornea. 2012;31(8):893–9.
55. Rao SK, Rajagopal R, Sitalakshmi G, Padmanabhan P. Limbal autografting: comparison of results in the acute and chronic phases of ocular surface burns. Cornea. 1999;18(2):164–71.
56. Chiesi Limited. Data on File: Notes from Meeting with Mr Alex Shortt, 22nd June 2016 (CHHOL20160794). July 2016.
57. Chiesi Limited. Data on File: Clinical Expert Opinion Questionnaire (CHHOL20160798), July 2016.
58. Huang T, Wang Y, Zhang H, Gao N, Hu a. Limbal Allografting From Living-Related Donors to Treat Partial Limbal Deficiency Secondary to Ocular Chemical Burns. Arch Ophthalmol. 2011;129(10):1267–73.
59. Satake Y, Higa K, Tsubota K, Shimazaki J. Long-term Outcome of Cultivated Oral Mucosal Epithelial Sheet Transplantation in Treatment of Total Limbal Stem Cell Deficiency. Ophthalmology. 2011;118:1524–30.
60. Han ES, Wee WR, Lee JH, Kim MK. Long-term outcome and prognostic factor analysis for keratolimbal allografts. Graefes Arch Clin Exp Ophthalmol. 2011;249(11):1697–704.
61. Liang L, Sheha H, Tseng SCG. Long-term outcomes of keratolimbal allograft for total limbal stem cell deficiency using combined immunosuppressive agents and correction of ocular surface deficits. Arch Ophthalmol. 2009;127(11):1428–34.
62. Sonmez B. Fibrin Glue – Assisted Sutureless Limbal Stem Cell Transplantation Surgery for the Treatment of Severe. Cornea. 2011;30(3):296–300.
63. Sejpal K, Yu F, Aldave AJ. The Boston Keratoprosthesis in the Management of Corneal Limbal Stem Cell Deficiency. Cornea. 2011;30(11):1.
64. Magalhães FP, Hirai FE, De Sousa LB, De Oliveira LA. Boston type 1 keratoprosthesis outcomes in ocular burns. Acta Ophthalmol. 2013;91:e432–6.
65. World Health Organisation. Socio economic aspects of blindness and visual impairment. [Internet]. 2016. Available from: http://www.who.int/blindness/economy/en/ (accessed January 2017).
66. Chiesi Limited. Data on File: Patient testimonials for LSCD (CHHOL20160852). August 2016.

67. Chiesi Limited. Data on file: Patient Case Study (CHHOL20160865). August 2016.
68. World Health Organisation. World Health Statistics [Internet]. 2016. Available from: http://www.who.int/gho/publications/world_health_statistics/EN_WHS08_Full.pdf (accessed January 2017).
69. Office for National Statistics. Statistical Bulletin. Annual mid-year population estimates, 2014. [Internet]. 2015. Available from: http://www.ons.gov.uk/ons/dcp171778_406922.pdf (accessed January 2017).
70. Medi-Pragma. Data on File: Limbal Stem Cell Deficiency Market Potential Analysis Summary Report, May 2012.
71. NICE. Corneal endothelial transplantation [IPG304] [Internet]. 2009. Available from: https://www.nice.org.uk/Guidance/IPG304 (accessed January 2017).
72. NICE. Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium [IPG216]. 2007;(April):1–2. Available from: https://www.nice.org.uk/Guidance/IPG216 (accessed January 2017).
73. NICE. Eye Conditions Overview [Internet]. 2015. Available from: http://pathways.nice.org.uk/pathways/eye-conditions (accessed January 2017).
74. Department of Health. Title: The NHS Outcomes Framework 2015/16. 2014;(December 2014). Available from: https://www.gov.uk/government/publications/nhs-outcomes-framework-2015-to-2016 (accessed January 2017).
75. NHS England. Manual for Prescribed Specialised Services 2013/14 [Internet]. 2016. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf (accessed January 2017).
76. NHS England. NHS STANDARD CONTRACT FOR SPECIALISED OPHTHALMOLOGY (ADULT) [Internet]. 2013. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/d12-spec-ophthalmo-ad.pdf (accessed January 2017).
77. NHS England. 2013/14 NHS STANDARD CONTRACT FOR OSTEO-ODONTO-KERATOPROSTHESIS SERVICE FOR CORNEAL BLINDNESS (ADULTS) [Internet]. 2013. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/d12-osteo-odonto-kerato.pdf (accessed January 2017).
78. Marchini G, Pedrotti E, Pedrotti M, Barbaro V, Di Iorio E, Ferrari S, et al. Long-term effectiveness of autologous cultured limbal stem cell grafts in patients with limbal stem cell deficiency due to chemical burns. Clin Exp Ophthalmol. 2012;40:255–67.
79. Pellegrini G, Traverso CE, Franzi AT, Zingirian M, Cancedda R, De Luca M. Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. Lancet. 1997;349(9057):990–3.
80. Pellegrini G, Rama P, Matuska S, Lambiase A, Bonini S, Pocobelli A, et al. Biological parameters determining the clinical outcome of autologous cultures of limbal stem cells. Regen Med. 2013;8(5):553–67.
81. Rama P, Bonini S, Lambiase A, Golisano O, Paterna P, De Luca M, et al. Autologous fibrin-cultured limbal stem cells permanently restore the corneal surface of patients with total limbal stem cell deficiency. Transplantation. 2001;72(9):1478–85.
82. Chiesi Farmaceutici S.p.A. Clinical study report No.: CCD-0918-CSR-0040.

Retrospective evaluation of the safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency (HLSTM02). 2012.
83. Chiesi Farmaceutici S.p.A. Clinical study report No.: CCD-GPLSCD01-04. Retrospective evaluation of the safety and efficacy of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with LSCD due to ocular burns (HLSTM04). 2014.
84. Fernandes M, Sangwan V, Rao S, Basti S, Sridhar M, Bansal A, et al. Limbal stem cell transplantation. Indian J Ophthalmol. 2004;52(1):5–22.
85. Rauz S, Saw VP. Serum eye drops, amniotic membrane and limbal epithelial stem cells-tools in the treatment of ocular surface disease. Cell Tissue Bank. 2010;11(1):13–27.
86. Schornack MM. Limbal stem cell disease: Management with scleral lenses. Clin Exp Optom. 2011;94(6):592–4.
87. Anderson DF. Amniotic membrane transplantation for partial limbal stem cell deficiency. Br J Ophthalmol. 2001;85(5):567–75.
88. Dua HS. The conjunctiva in corneal epithelial wound healing. Br J Ophthalmol. 1998;82(12):1407–11.
89. Kheirkhah A, Johnson D, Paranjpe D, Raju V, Casas V, Tseng S. Temporary sutureless amniotic membrane patch for acute alkaline burns. Arch Ophthalmol. 2008;126(6):1059–66.
90. Dua HS, Azuara-Blanco A. Autologous limbal transplantation in patients with unilateral corneal stem cell deficiency. Br J Ophthalmol. 2000;84:273–8.
91. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. Ophthalmology. 1989;96(5):709-22-3.
92. Moldovan S, Borderie V, Baudrimont M, Laroche L. Treatment of unilateral limbal stem cell deficiency syndrome by limbal autograft. J Fr Ophtalmol. 1999;22(3):302–9.
93. Eslani M, Baradaran-Rafii A, Movahedan A, Moss A, Holland E, Djalilian A. Late acute graft rejection after keratolimbal allograft. Am Acad Ophthalmol. 2015;PO051.
94. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. Trans Am Ophthalmol Soc. 1996;94:677–743.
95. Ilari L, Daya SM. Long-term outcomes of keratolimbal allograft for the treatment of severe ocular surface disorders. Ophthalmology. 2002;109(7):1278–84.
96. Maruyama-Hosoi F, Shimazaki J, Shimmura S, Tsubota K. Changes observed in keratolimbal allograft. Cornea. 2006;25(4):377–82.
97. Tsai RJ, Tseng SC. Human allograft limbal transplantation for corneal surface reconstruction. Cornea. 1994;13(5):389–400.
98. Tsubota K, Toda I, Saito H, Shinozaki N, Shimazaki J. Reconstruction of the corneal epithelium by limbal allograft transplantation for severe ocular surface disorders. Ophthalmology. 1995;102(10):1486–96.
99. Borderie V, Touzeau O, Bourcier T, Allouch C, Scheer S LL. Treatment of the sequelae of ocular burns using limbal transplantation. J Fr Ophtalmol. 2003;26(7):710–6.
100. Ivekovic R, Tedeschi-Reiner E, Novak-Laus K, Andrijevic-Derk B, Cima I, Mandic Z. Limbal graft and/or amniotic membrane transplantation in the treatment of ocular burns. Ophthalmologica. 2005;219(5):297–302.
101. Meallet M, Espana E, Grueterich M, Ti S-E, Goto E, Tseng S. Amniotic

Membrane Transplantation with Conjunctiva! Limbal Autograft for Total Limbal Stem Cell Deficiency. Ophthalmology. 2003;110:1585–92.
102. Solomon A, Ellies P, Anderson DF, Touhami A, Grueterich M, Espana EM, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. Ophthalmology. 2002;109(6):1159–66.
103. Tan DT, Ficker LA, Buckley RJ. Limbal transplantation. Ophthalmology. 1996;103(1):29–36.
104. Torres J, Fernández I, Quadrado MJ, Murta J, Herreras J, Rodríguez-Ares MT, et al. Limbal transplantation: multicenter retrospective case series analysis. Arch Soc Esp Oftalmol. 2008;83:417–22.
105. Joanna Briggs Institute. Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. Checklist for Case Series. [Internet]. 2016. Available from: http://joannabriggs.org/research/critical-appraisal-tools.html (accessed January 2017).
106. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
107. Milazzo G, De Luca M, Pellegrini G. Holoclar: first of its kind in more ways than one. Cell Gene Ther Insights. 2016;2(2):183–97.
108. Fordham R, Ciminata G, Madoni A, Magni T, Ardigò D, Pelosi D. Cost-effectiveness analysis of ex-vivo expanded autologous corneal epithelial cells containing stem cells to repair the damaged ocular surface in patients with moderate to severe limbal stem cell deficiency due to ocular burns in the UK. In: The ISPOR Scientific Presentations Database. 2015.
109. Fielding S, Cummins E, Cruickshank M, Fraser C, Lois N, Brazzelli M. Aflibercept for treating diabetic macular oedema. 2014.
110. Hirneiss C. The impact of a better-seeing eye and a worse-seeing eye on vision-related quality of life. Clin Ophthalmol. 2014;8:1703–9.
111. Finger RP, Fenwick E, Hirneiss CW, Hsueh A, Guymer RH, Lamoureux EL, et al. Visual impairment as a function of visual acuity in both eyes and its impact on patient reported preferences. PLoS One. 2013;8(12):e81042.
112. Vu HT V, Keeffe JE, McCarty CA, Taylor HR. Impact of unilateral and bilateral vision loss on quality of life. Br J Ophthalmol. 2005;89(3):360–3.
113. Rahi JS, Cumberland PM, Peckham CS. Visual Impairment and Vision-Related Quality of Life in Working-Age Adults. Findings in the 1958 British Birth Cohort. Ophthalmology. 2009;116(2):270–4.
114. Vashist P, Gupta N, Tandon R, Gupta SK, Dwivedi S, Mani K. Population-based assessment of vision-related quality of life in corneal disease : results from the CORE study. Br J Ophthalmol. 2016;100(5):588–93.
115. Bass EB, Marsh MJ, Mangione CM, Bressler NM, Childs AL, Dong LM, et al. Patients' perceptions of the value of current vision: assessment of preference values among patients with subfoveal choroidal neovascularization--The Submacular Surgery Trials Vision Preference Value Scale: SST Report No. 6. Arch Ophthalmol. 2004;122(12):1856–67.
116. Brown MM, Brown GC, Sharma S, Busbee B, Brown H. Quality of life associated with unilateral and bilateral good vision. Ophthalmology. 2001;108(4):643–7.
117. Brown MM, Brown GC, Brown HC, Irwin B, Brown KS. The comparative effectiveness and cost-effectiveness of vitreoretinal interventions. Curr Opin Ophthalmol. 2008;19(3):202–7.

118. Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss: A time tradeoff utility analysis comparison with medical health states. Ophthalmology. 2003;110(6):1076–81.
119. Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. Am J Ophthalmol. 1999;128(3):324–30.
120. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value Heal. 2009;12(5):793–9.
121. Dua HS, Azuara-Blanco A. Limbal stem cells of the corneal epithelium. Surv Ophthalmol. 2000;44(5):415–25.
122. Chiesi Ltd. Data on file. Minutes of Clinical Advisory Board Meeting 30th October 2015 (CHHOL20150567g). July 2016.

# 8 Appendices

Appendix 1: Chiesi Farmaceutici S.p.A. Holoclar 79,000-316,000 cells/cm$^2$ living tissue equivalent Summary of Product Characteristics, December 2015.

Appendix 2: European Medicines Agency. Assessment report: Holoclar (EMA/25273/2015), 18 December 2014.

Appendix 3: Chiesi Limited. Educational Manual for the Screening and Treatment of Pre- and Post-Operative Patients Undergoing an Autologous Transplant of the Corneal Epithelium Reconstructed from Stem Cells (CLC014/1).

Appendix 4: Holoclar systematic review report (CHHOL20160799). July 2016.

Appendix 5: Holoclar model – unilateral.

Appendix 6: Holoclar model – bilateral.

Appendix 7: York Health Economics Consortium. Standard Gamble to Derive Utility Health States for Limbal Stem Cell Deficiency. July 2016.

Appendix 8: Sensitivity analysis models.

Appendix 9: Base Case and Sensitivity Analyses with Holoclar Undiscounted List Price.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

**Single technology appraisal**

**Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]**

Dear [redacted] and [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group, University of Liverpool, and the technical team at NICE have looked at the submission received on 8 August from Chiesi. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 15 September 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Irina Voicechovskaja, Technical Lead (Irina.Voicechovskaja@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.Yates@nice.org.uk).

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

**Section A: Clarification on effectiveness data**

A1. **Priority Question**: Please provide copies of the protocols and statistical analysis plans for the Holoclar studies HLSTM01, HLSTM02, HLSTM04

A2. **Priority Question:** Please explain the relationship and/or any overlap between the patient population reported in the published studies (Marchini 2012, Pellegrini 1997, Pellegrini 2013, Rama 2001 and Rama 2010) and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies.

A3. In Section 4.11.1 of the company submission (CS), it is reported that in the systematic review of evidence for the effectiveness of Holoclar, 8 studies were identified as relevant. Of the 8 studies, 5 are published (Marchini 2012, Pellegrini 1997, Pellegrini 2013, Rama 2001 and Rama 2010) and 3 were provided by the company. The ERG notes that none of the 5 published studies report that the product used to treat patients was Holoclar/ GPLSCD01. Please explain how these studies were identified as studies of Holoclar.

A4. In Section 4.11.1 and in Figure 8 of the CS, it is reported that in the systematic review of evidence for the effectiveness of comparator technologies, 25 studies were identified as relevant and that the 25 studies are described in Table 12 of the CS. The ERG notes that 28 distinct studies are described in Table 12 of the CS. Please clarify.

A5. In Section 4.11.4 of the CS, the first paragraph (page 122) begins with 'In contrast, the criteria for success for Holoclar were pre-defined and are consistent with those used in clinical practice…..' Please clarify whether this pertains to ALL Holoclar studies (published and unpublished) or only to the HLSTM01 study.

A6. In Section 4.11.4 of the CS, it is stated that 'The selection criteria in study HLSTM01 were modelled on the original study….' Please explain what 'the original study' refers to.

A7. In Section 4.11.4 of the CS, it is stated that 'Two published studies included 25 of these remaining 82 patients (12 and 13 respectively)'.

i) The references cited are 78 (Marchini 2012) and 108 (De Luca 2006). Is the De Luca reference correct?
ii) From Table 2 of the Marchini 2012 study, please indicate which 12 patients provided the outcomes that were compared with the outcomes of patients in the HLSTM01 study. Please do the same for the De Luca (or relevant) study.

A8. In Section 4.11.4 of the CS, it is reported that investigators declined the invitation to participate in the HLSTM01 study and decided not to release the clinical data pertaining to 82 patients treated with Holoclar. Please provide the reasons given by the investigators for their non-participation.

A9. The ERG notes from the EPAR for Holoclar (EPAR p45) that 3 patients in the HLSTM01 study and 2 patients in the HLSTM02 study were paediatrics. In the scope issued

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

by NICE, the patient population to be considered is adults. Please indicate how the removal of the paediatric data affects the overall results of HLSTM01 and HLSTM02.

A10. In Section 4.11.15 of the CS (page 126/7) the results of an independent assessment of the outcomes for 46 patients in the HLSTM01 study are reported. Please indicate whether the 31 cases considered a success in the independent assessment were the same cases that were considered a success by the study investigators.

**Section B: Clarification on cost-effectiveness data**

B1. **Priority question:** Please provide all patient level data from HLSTM01 that were used to generate the effectiveness evidence in section 5.3 of the CS. Please indicate whether patients had unilateral or bilateral limbal stem cell deficiency.

B2. **Priority question:** Please provide the specific question in the HLSTM01 trial that provided data for Table 27 of the CS.

B3. **Priority question**: In the base case, patients without stromal scarring have the same utility decrement for disfigurement as those with stromal scarring. Please provide details for this rationale.

B4. **Priority question**: Please provide further evidence (if available) as to:

i) The expected number of flare ups (per patient) per year that would require treatment and
ii) Why each flare would be treated with autologous eye drops.

B5. **Priority question:** In the company model, two bottles of autologous serum eye drops are required during the stable phase in the first 12 months post-operation for all patients except those treated with Holoclar. Please explain why patients treated with Holoclar do not use autologous serum eye drops.

B6. **Priority question:** Please clarify how many bottles of autologous serum eye drops are required, per patient, post-operatively during the first 12 months? The company model includes two bottles, whereas the information provided in the CS (page 64, page 223) is contradictory.

B7. There are inconsistencies on resource use in several areas between the CS and the model. Please provide information and the source of information for each procedure on

i) The number of outpatient appointments required
ii) The requirement for bandage contact lenses
iii) The requirement for a biopsy
iv) Daily frequency and duration of steroid eye drops, artificial tears and antibiotic eye drops following each procedure.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

B8. The model uses a 90% extraction success rate for Holoclar and a 100% success rate for the comparator extractions/biopsies. Please provide the sources for these data points, or a rationale if these are assumptions.

B8. Will all patients who fail a first treatment with Holoclar be offered a second treatment within 12 months? If the second treatment also fails, would a third treatment be offered within another 12 months? Is this sufficient time to allow the treated eye to recover?

B9. In Section 5.1 of the CS, the company provides a short critique of the single published cost-effectiveness study identified in the systematic review. The details of the analysis given by the company are not available to the ERG in the published abstract. Please provide a more comprehensive report of the analysis

**Section C: Textual clarifications and additional points**

C1. Is there a publication date for the HLSTM01 study?

C2. In Section 4.2 of the CS, the company provides reasons for the absence of randomised controlled trials (RCTs) in this patient group. Does the company consider that a plausible control group could consist of patients who receive conservative management with the removal of eye surface and application of the carrier without cells?

C3. Please confirm if the first safety update report for Holoclar (due 6 months after approval by the EMA) has been submitted to the EMA.

**CHIESI LIMITED**
Manchester Green,
333 Styal Road,
Manchester M22 5LG
Tel: 0161 488 5555
Fax: 0161 488 5566
info.uk@chiesi.com

Frances Sutcliffe
Associate Director, Appraisals
Centre for Health Technology Evaluation
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BT

15th September 2016

**Single Technology Appraisal**
**Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]**

Dear Frances,

In reply to your recent request for further clarification on specific aspects of the clinical and cost effectiveness data contained in the above company submission, please find enclosed the responses from Chiesi. We trust that these responses will assist the ERG and the technical team at NICE to address these issues in their reports.

As requested, two versions of Chiesi's responses are submitted; one with academic/ commercial-in-confidence information clearly marked and one with this information removed. We have underlined all confidential information, and separately highlighted information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow. The checklist for confidential information has also been completed and is enclosed describing data that are not already referenced in the main body of our submission and that are academic/commercial in confidence.

If you have any further queries or require any additional clarification on the issues raised then please do not hesitate to contact me.

Yours sincerely,

Greg Amatt
Head of Rare Diseases UK & Ireland
Chiesi Limited

## Section A: Clarification on effectiveness data

**A1. Priority Question: Please provide copies of the protocols and statistical analysis plans for the Holoclar studies HLSTM01, HLSTM02, HLSTM04.**

As requested, please find enclosed copies of the protocols and statistical analysis plans for the Holoclar studies HLSTM01, HLSTM02, HLSTM04 (enclosures 1-6).

**A2. Priority Question: Please explain the relationship and/or any overlap between the patient population reported in the published studies (Marchini 2012, Pellegrini 1997, Pellegrini 2013, Rama 2001 and Rama 2010) and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies.**

The five publications report data from research conducted independently by the authors. The studies were designed and protocols developed directly by the investigators. The studies were planned and conducted prior to the adoption and implementation of the Advanced Therapy Medicinal Products Regulation (EC) No. 1394/2007 and the subsequent classification of Holoclar as a Tissue Engineered Product. Subsequent to this classification, Chiesi undertook a rigorous analysis of all the available clinical data based upon the use of Holoclar.

Overlap between the patient populations is as follows:

- Pellegrini 1997 – there is no overlap between the patient population reported in this pilot study and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies.
- Rama 2001 – 6 of the 18 patients whose results are included in this publication were also included in the HLSTM01 study. There is no overlap between the patient population reported in Rama 2001 and the patient populations reported in the HLSTM02 and HLSTM04 studies.
- Rama 2010 – 93 of the 112 patients whose results are included in this publication were also included in the HLSTM01 study. There is no overlap between the patient population reported in Rama 2010 and the patient populations reported in the HLSTM02 and HLSTM04 studies.
- Marchini 2012 – there is no overlap between the patient population reported in this study and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies.
- Pellegrini 2013 – there is almost complete overlap between the patient population reported in this study and the patient populations reported in the HLSTM01 and HLSTM02 studies. Out of the 152 patients included in the publication, 133 are included in the studies HLSTM01 and HLSTM02 studies. There is no overlap between the patient population reported in Pellegrini 2013 and the patient population reported in the HLSTM04 studies.

**A3. In Section 4.11.1 of the company submission (CS), it is reported that in the systematic review of evidence for the effectiveness of Holoclar, 8 studies were identified as relevant. Of the 8 studies, 5 are published (Marchini 2012, Pellegrini 1997, Pellegrini 2013, Rama 2001 and Rama 2010) and 3 were provided by the company. The ERG notes that none of the 5 published studies report that the product used to treat patients was Holoclar/GPLSCD01. Please explain how these studies were identified as studies of Holoclar.**

Much of the initial research into stem cells and their potential clinical application for tissue engineering and regeneration stemmed from the considerable interests in academic institutions. Similarly, the development of what was ultimately to become Holoclar (subsequent to the implementation of the Advanced Therapy Medicinal Products Regulation (EC) No. 1394/2007) began over a decade previously in the early 1990s through the independent research carried out by two Italian scientists, Professor Michele De Luca and Professor Graziella Pellegrini. Then known as 'autologous cultured corneal sheets', the initial version of Holoclar was used for the first time in 1995 to treat two patients with limbal stem cell deficiency resulting from chemical burns. Results of this early pilot study were published in Lancet in 1997 by Pellegrini *et al* (Pellegrini 1997).

Following this initial proof-of-concept study, certain modifications were made to the initial Holoclar product in respect of its composition, including replacement of the previous supporting material with a layer of human fibrin for cell attachment. It is this modified form that is representative of the composition of the finished Holoclar product intended for commercialisation. All subsequent studies, including the other four published studies and the HLSTM01, HLSTM02 and HLSTM04 studies, examine the effects of this form of Holoclar.

As with any medicinal product, the brand name of the product is only finally agreed at the time of a Marketing Authorisation (February 2015). Therefore the other four published studies that were authored independently of Chiesi by their academic investigators (Rama 2001, Rama 2010, Marchini 2012 and Pellegrini 2013), variably refer to Holoclar as 'autologous fibrin-cultured limbal stem cells' (Rama 2001), 'autologous limbal stem cells cultivated on fibrin' (Rama 2010), 'autologous limbal stem cells grown onto 3T3 feeder layers and fibrin' (Marchini 2012) and as 'autologous limbal cells cultured on fibrin and clinical-grade 3T3-J2 feeder cells' (Pellegrini 2013). It is with this background knowledge of the development of Holoclar that the five published studies were identified when screening the results of the literature search as part of the systematic review.

**A4. In Section 4.11.1 and in Figure 8 of the CS, it is reported that in the systematic review of evidence for the effectiveness of comparator technologies, 25 studies were identified as relevant and that the 25 studies are described in Table 12 of the CS. The ERG notes that 28 distinct studies are described in Table 12 of the CS. Please clarify.**

There are 28 distinct studies listed in Table 12 of the company submission. The systematic literature review carried out using the search strings defined within the protocol identified 25 of these studies for the comparator technologies. In addition, a further three studies were identified as cross-references within Liang 2009 (reference 61). These were as follows: Maruyama-Hosoi 2006 (reference 96 in the company submission), Tan 1996 (reference 103 in the company submission) and Tsubota 1995 (reference 98 in the company submission). For all relevant entries in table 12 of the company submission, this is indicated by bold highlighted text stating, "NB Cross-referenced from Liang, Arch Ophthalmol 2009".

**A5. In Section 4.11.4 of the CS, the first paragraph (page 122) begins with 'In contrast, the criteria for success for Holoclar were pre-defined and are consistent with those used in clinical practice…..' Please clarify whether this pertains to ALL Holoclar studies (published and unpublished) or only to the HLSTM01 study.**

This comment pertains to the seven Holoclar studies that are discussed in detail within section 4.11, i.e. to the three unpublished company-sponsored Holoclar studies, i.e. HLSTM01, HLSTM02 and HLSTM04 and additionally to Marchini 2012, Pellegrini 2013, Rama 2001 and Rama 2010.

The remaining study, Pellegrini 1997, was a pilot study only and provided no data relevant to the outcome measures identified in the scope. As discussed on pages 74-75 of the company submission, this paper was excluded from subsequent detailed discussion and the comment cited in the question does not therefore apply to this study.

**A6. In Section 4.11.4 of the CS, it is stated that 'The selection criteria in study HLSTM01 were modelled on the original study...' Please explain what 'the original study' refers to.**

The original study is the study published by Rama *et al* in the New England Journal of Medicine in 2010, previously supplied with the company submission as reference 8 (Rama 2010).

**A7. In Section 4.11.4 of the CS, it is stated that 'Two published studies included 25 of these remaining 82 patients (12 and 13 respectively)'.**

**i) The references cited are 78 (Marchini 2012) and 108 (De Luca 2006). Is the De Luca reference correct?**

**ii) From Table 2 of the Marchini 2012 study, please indicate which 12 patients provided the outcomes that were compared with the outcomes of patients in the HLSTM01 study. Please do the same for the De Luca (or relevant) study.**

i) The reference to 108 (De Luca 2006) is an error. The correct references are 78 (Marchini 2012) and 81 (Rama 2001). Additionally we would like to clarify that of the 25 patients referred to, it is 13 patients that are included in the Marchini 2012 study and 12 patients that are included in the Rama 2001 study.

ii) The 25 patients that provided outcomes data for treatment with Holoclar that were not included and could be compared with the outcomes of the patients in the HLSTM01 study are as follows:

Rama *et al* (Transplantation 2001)

This publication reports the results of Holoclar treatment in 18 patients (mean age 48 ±12 years) with moderate or severe limbal stem cell deficiency secondary to chemical burns. Six of the 18 patients were included in the HLSTM01 study. Data from the remaining 12 patients was available for comparison with the data collected in HLSTM01. From table 1 presented in the Rama 2001 publication, these 12 patients are patients 1-7, 11 and 14-17.

Marchini *et al* (Clinical and Experimental Ophthalmology 2012)

This publication reports results of a prospective, non-comparative, interventional case series including 16 patients (median age 47.5 years) with limbal stem cell deficiency due to chemical burns. None of the 16 patients were included in the HLSTM01 study. Data from 13

patients was available for comparison with the data collected in HLSTM01. From table 2 presented in the Marchini 2012 publication, these 13 patients are patients 1-13.

**A8. In Section 4.11.4 of the CS, it is reported that investigators declined the invitation to participate in the HLSTM01 study and decided not to release the clinical data pertaining to 82 patients treated with Holoclar. Please provide the reasons given by the investigators for their non-participation.**

The investigator(s) involved with the treatment of this subset of patients, although formally invited by Chiesi to participate in the HLSTM01 study, declined to participate. Declinations were proffered in written or verbal form or alternatively, no response to repeated invitations was also considered to be a declination. Where investigator permission for the use of patient data was declined, these patients were correspondingly excluded from any retrospective analyses performed as part of the HLSTM01 study. The reason for an investigator declining the invitation to participate in the HLSTM01 study was not requested nor required to be stated, only that the invitation had been declined.

**A9. The ERG notes from the EPAR for Holoclar (EPAR p45) that 3 patients in the HLSTM01 study and 2 patients in the HLSTM02 study were paediatrics. In the scope issued by NICE, the patient population to be considered is adults. Please indicate how the removal of the paediatric data affects the overall results of HLSTM01 and HLSTM02.**

In 2 of the 5 paediatric patients, treatment outcome was successful and accompanied by improvement in visual acuity and/or clinical symptoms (when present at baseline), while 2 of the 5 paediatric patients with severe corneal neovascularisation were considered as treatment failures. Given the extremely limited number of paediatric patients included in the HLSTM01 and HLSTM02 studies and the fact that the overall success rate was lower in the paediatric population compared to the overall population treated (2 out of 5 successes, corresponding to 40%), the removal of the paediatric data will not negatively affect the efficacy results of studies HLSTM01 and HLSTM02.

**A10. In Section 4.11.15 of the CS (page 126/7) the results of an independent assessment of the outcomes for 46 patients in the HLSTM01 study are reported. Please indicate whether the 31 cases considered a success in the independent assessment were the same cases that were considered a success by the study investigators.**

There was concordance between the assessments of the investigator and blinded assessor in 36/46 cases (consisting of 28 cases with a successful clinical outcome and 8 cases with a failed clinical outcome). There was discordance between investigator and blinded assessor in 10/46 cases, of which 3 failures (investigator assessment) were deemed successes by blinded assessment and 7 successes (investigator assessment) were deemed failures by blinded assessment.

**Section B: Clarification on cost-effectiveness data**

**B1. Priority question: Please provide all patient level data from HLSTM01 that were used to generate the effectiveness evidence in section 5.3 of the CS. Please indicate whether patients had unilateral or bilateral limbal stem cell deficiency.**

As requested, please find enclosed all patient level data from the HLSTM01 study that were used to generate the effectiveness evidence. All trial data are provided in their original form as described by the Case Report Form (CRF) for the HLSTM01 study, a copy of which is also enclosed (enclosure 7). All SAS programming used to inform Section 5.3 of the company submission from data cleaning and manipulation to regression models (including sensitivity regressions) and construction of data outputs are included (in MSExcel format). Copies of original data plus the constructed data are included, together with an MSWord document which explains the process and headings (enclosure 8).

It is not possible to indicate whether patients included in the HLSTM01 study had unilateral or bilateral limbal stem cell deficiency as this was not recorded in the CRF or otherwise reported in the HLSTM01 study. However, what is known is that only one patient with bilateral LSCD was treated with Holoclar in both eyes. Both unilateral and bilateral excel models are therefore based on the assumption that the success of transplant and the impact of the success of transplant (conditional on presence or absence of stromal scarring and underlying VA) on the VA of the treated eye, as estimated using HLSTM01 data, is independent of the VA of the other eye. However, the expected utility for the individual will be a function of the VA in both eyes.

**B2. Priority question: Please provide the specific question in the HLSTM01 trial that provided data for Table 27 of the CS.**

Table 27 was created from patient responses to questions 10 through 12 on page 4 of the Case Report Form (CRF) for the HLSTM01 study, which documents the extent of pain, burning and photophobia respectively at the pre-surgical visit. As mentioned above, a copy of the CRF is enclosed for your information.

The original data are contained in data file ce21 in variables EXEYE10 (Y/N presence of pain) to YESP12 (level of photophobia [mild/moderate/severe] if present). Any legitimate response to the level of pain/burning/photophobia taken from the YESPxx question was used as the level of symptom endured by the patient. In the absence of a value in the YESPxx question a value of ‘None’ was assigned. In the event that both EXEYExx and YESPxx were missing, a missing value was assigned to the variable tabulated in table 27.

**B3. Priority question: In the base case, patients without stromal scarring have the same utility decrement for disfigurement as those with stromal scarring. Please provide details for this rationale.**

There is no accepted clinical definition of disfigurement for this clinical setting, i.e. limbal stem cell deficiency. Therefore, Chiesi have taken clinical expert advice, which identified three parameters from the endpoints recorded in the HLSTM01 study (namely corneal opacity, superficial corneal neovascularisation and inflammation) that would most appropriately serve as a proxy for disfigurement.

As such we have fitted this into the model by matching it to the structure of the model and the states modelled over time. We have assumed that a lack of corneal neovascularisation and inflammation are captured by establishing a stable corneal surface (i.e. treatment success) and corneal opacity is the variable, which captures the presence or absence of stromal scarring. We have consequently assumed that if either stromal scarring or an unstable ocular surface is present, then there is disfigurement.

**B4. Priority question: Please provide further evidence (if available) as to:**

**i) The expected number of flare ups (per patient) per year that would require treatment and**

**ii) Why each flare would be treated with autologous eye drops.**

As there are no published data that adequately describe these issues, Chiesi obtained clinical expert opinion, previously supplied in the company submission as reference 57 (Chiesi 2016 CHHOL20160798), in order to inform on these points. Expert opinion indicates the following:

i) Typically 90% of patients experience at least one flare per year and 50% of patients experience two flares per year. All flares require treatment as they typically result in an epithelial defect, which is a serious complication of limbal stem cell deficiency and a potential ophthalmic emergency. Flares typically occur 1-2 per year per patient with moderate to severe limbal stem cell deficiency, and are typically of 6-8 weeks duration.

ii) During a flare, patients typically develop an epithelial defect or other active problem associated with limbal stem cell deficiency, which requires aggressive medical intervention. Typically, this is initially managed in hospital with a typical duration of hospitalisation of 5-7 days. Up to 10% of cases will require surgical management of their flare.

Treatment of a flare (best supportive care) includes topical steroids, ocular lubricants, bandage contact lens, oral vitamin C, oral/topical antibiotics and autologous serum eye drops. Treatment of a flare typically lasts 2 months before stability of the ocular surface is achieved/restored. It is estimated that best supportive care typically costs the NHS £7.5k per year per patient. A significant portion of this cost will be for the treatment of flares.

**B5. Priority question: In the company model, two bottles of autologous serum eye drops are required during the stable phase in the first 12 months post-operation for all patients <u>except</u> those treated with Holoclar. Please explain why patients treated with Holoclar do not use autologous serum eye drops.**

As described in section 2.3 (page 32) of the company submission and also in the Summary of Product Characteristics for Holoclar, all that is required in the postoperative phase following treatment with Holoclar is an appropriate regimen of topical and systemic anti-inflammatory and prophylactic antibiotic treatment. Autologous serum eye drops were not used during clinical trials of Holoclar and are not required for the use of Holoclar.
Expert opinion was obtained regarding the management of moderate to severe LSCD using CLAU, lr-CLAL and KLAL and the associated postoperative care for both the donor and recipient eyes. This is described in the previously supplied reference 56 (Chiesi 2016

CHHOL20160794) of the company submission. For all three comparators, CLAU, lr-CLAL and KLAL, expert opinion indicates that autologous serum eye drops are required postoperatively in the recipient eye for a period of 3 months post-procedure. As expert opinion indicates that each batch/bottle of autologous serum eye drops lasts 60 days then two batches/bottles will be required to cover a 3-month treatment period.

**B6. Priority question: Please clarify how many bottles of autologous serum eye drops are required, per patient, post-operatively during the first 12 months? The company model includes two bottles, whereas the information provided in the CS (page 64, page 223) is contradictory.**

As stated in the response to question B5 above, each batch/bottle of autologous serum eye drops lasts 60 days. Therefore two batches/bottles will be required to cover a 3-month treatment period. The information presented on page 64 of the company submission (which relates to CLAU) does not therefore contradict, as each patient will require two batches/bottles. Their use will be in the first 3 months after the surgical procedure for CLAU, lr-CLAL and KLAL.

**B7. There are inconsistencies on resource use in several areas between the CS and the model. Please provide information and the source of information for each procedure on**

- **i) The number of outpatient appointments required**
- **ii) The requirement for bandage contact lenses**
- **iii) The requirement for a biopsy**
- **iv) Daily frequency and duration of steroid eye drops, artificial tears and antibiotic eye drops following each procedure.**

For Holoclar, this information is contained in section 2.3 of the company submission and is also described in the Holoclar Summary of Product Characteristics. As there are no published data that adequately describe these issues for the comparators, Chiesi obtained clinical expert opinion, previously supplied in the company submission as reference 56 (Chiesi 2016 CHHOL20160794) in order to inform on these points for the comparator technologies. This information is contained in section 3.7 of the company submission.

i) Holoclar must be followed by an appropriate clinical monitoring schedule. Follow-up visits should be performed according to clinical judgement. The suggested schedule for outpatient appointments is for follow-up visits at 3 days, 14 days, 45 days, 6 months and 12 months after receiving treatment with Holoclar.

   For CLAU the suggested schedule for outpatient appointments is for follow-up visits at 1 week, 14 days (for reversal of tarsorrhaphy) and then every 4 weeks until a stable, intact epithelium is obtained (usually at 3 months post-op). Once the epithelium is stable, outpatient review is required 1-2 monthly up to a year. Patients remain on annual review thereafter.

   For lr-CLAL, the suggested schedule for outpatient appointments for the recipient patient essentially follows the same schedule as for CLAU above. However, additional outpatient appointments will be required to provide follow-up for the live

related donor. Typically the live related donor would be followed up for the first 4-8 weeks (as per previous schedule for CLAU) with an additional follow-up appointment at 6 months to check that the donation procedure has not caused limbal stem cell deficiency or any other long-term sequelae in the donor eye.

For KLAL, the suggested schedule for outpatient appointments essentially follows the same schedule as for CLAU above. However, as the patient also requires additional post-operative immunosuppression with sirolimus plus rapamycin, this will require assessment of baseline renal function and subsequent renal monitoring whilst on therapy. Treatment and hence this additional treatment monitoring will continue until the graft fails.

ii) Given the large amount of tissue that must be removed from the donor eye for CLAU and lr-CLAL, a bandage contact lens is required for the ***donor eye*** in all patients undergoing CLAU and in all relatives providing tissue for lr-CLAL in order to cover the epithelial defect created. A bandage contact lens requires changing every 8 weeks until healing has occurred. A bandage contact lens is not required for treatment with Holoclar (where the biopsy size is much smaller) or KLAL (where the donor is cadaveric).

iii) Biopsy of the patient's donor eye is a specific surgical procedure unique to Holoclar and is required for the manufacture of Holoclar. Assuming successful manufacture, Holoclar is implanted several weeks after the initial biopsy into the same patient's recipient eye during a separate surgical procedure.

For CLAU the equivalent process (extraction of the conjunctival limbal autograft from the patient's donor eye) occurs as part of the same surgical procedure as transplantation of tissue into the patient's recipient eye, therefore there is no additional surgical procedure or procedural cost required. For KLAL, the equivalent process (extraction of the keratolimbal allograft from a cadaver) does not involve the patient and the associated procedural cost can be assumed to be included in the cost of procuring the cadaveric allograft. For lr-CLAL, the equivalent process (extraction of the conjunctival limbal autograft from the donor eye of a living relative) requires a separate surgical procedure to remove the allograft from a live relative, although the two surgical procedures, i.e. extraction of tissue from the donor and transplantation of tissue to the patient, will be timed to coincide so transplantation can take place without delay. A separate surgical procedure and procedural cost will therefore be required.

iv) For Holoclar, an appropriate regimen of topical and oral anti-inflammatory and prophylactic antibiotic treatment must be given after the implantation procedure. In addition to oral steroid (for 4 weeks after implantation) and an oral antibiotic (for 2 weeks after implantation) the drops that are required (starting two weeks after implantation) are preservative-free dexamethasone 0.1% eye-drops, 1 drop three times per day for 2 weeks, then reduced to 1 drop twice daily for 1 week and 1 drop once daily for a further week. The topical corticosteroid can be maintained in case of persistent ocular inflammation.

For CLAU, (in addition to amniotic membrane transplantation and tarsorrhaphy for the recipient eye, a bandage contact lens for the donor eye, plus oral steroids and omeprazole) the drops required for the ***recipient eye*** are autologous serum eye drops for a period of 3 months, topical steroid eye drops, topical antibiotic eye drops and lubricant eye drops; and the drops that are required for the ***donor eye*** are: antibiotic eye drops for 2-4 weeks, topical steroid eye drops for 2-4 weeks and lubricant eye drops.

For lr-CLAL, similar post-operative regimen is required. The patient receives (in addition to the amniotic membrane transplantation, tarsorrhaphy, oral steroids and omeprazole) autologous serum eye drops for a period of 3 months, topical steroid eye drops, topical antibiotic eye drops and lubricant eye drops. The related donor receives (in addition to a bandage contact lens) antibiotic eye drops for 2-4 weeks, topical steroid eye drops for 2-4 weeks and lubricant eye drops.

For KLAL, the patient receives (in addition to the amniotic membrane transplantation, tarsorrhaphy, oral steroids, omeprazole, sirolimus and rapamycin) autologous serum eye drops for a period of 3 months, topical steroid eye drops, topical antibiotic eye drops and lubricant eye drops.

We are aware of the inconsistencies in the model to which you refer. Having corrected these, we do not believe this has a substantive impact on the results.

**B8. The model uses a 90% extraction success rate for Holoclar and a 100% success rate for the comparator extractions/biopsies. Please provide the sources for these data points, or a rationale if these are assumptions.**

For Holoclar, the 90% extraction success rate was based on the experience of past treatments by the manufacturer, Holostem Terapie Avanzate. Holoclar is released by the manufacturer only if sufficient number of stem cells (measured as p63 bright cells, the main functional component of Holoclar) are present to meet pre-specified quality standards, as required in the authorised manufacturing specification of Holoclar. In some cases it may be possible that the source limbal stem cells from the patient biopsy are not expandable or that the release criteria are not met, due to poor biopsy quality, patient characteristics or manufacturing failure.

Chiesi has been unable to identify any data on failed biopsy rates for CLAU, lr-CLAL and KLAL and, therefore, have adopted the conservative assumption of 100% biopsy success rates for these comparators.

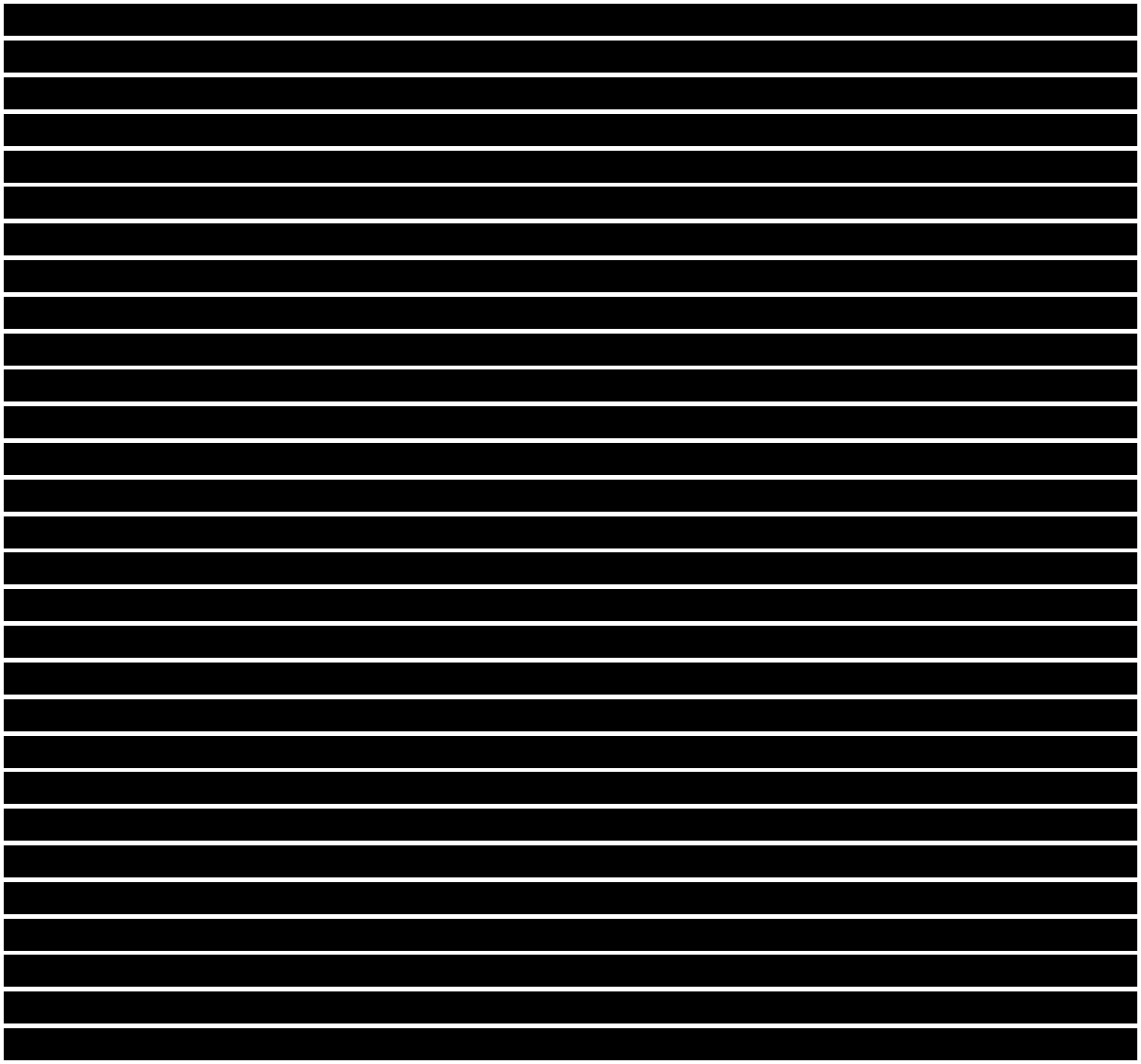
**B8. Will all patients who fail a first treatment with Holoclar be offered a second treatment within 12 months? If the second treatment also fails, would a third treatment be offered within another 12 months? Is this sufficient time to allow the treated eye to recover?**

Chiesi notes that this is the second question identified as B8.

The Summary of Product Characteristics for Holoclar states that, "The treatment may be repeated if considered indicated by the treating physician." The company considers that 12 months is a sufficient time to allow for both the treated eye to recover prior to re-treatment and for assessment as to whether treatment with Holoclar has been successful (or not). This latter point is illustrated by the Kaplan-Mayer chart presented in figure 12 of the company submission (taken from Figure 1 of the publication by Rama 2010 and previously supplied with the company submission as reference 8). This clearly indicates that in all cases where treatment failure occurs with Holoclar, it will become apparent within the first 12 months after treatment.

Similarly, if the first re-treatment with Holoclar fails, the expectation is that a second re-treatment could be performed, if considered indicated by the treating physician, within a similar time frame.

**B9. In Section 5.1 of the CS, the company provides a short critique of the single published cost-effectiveness study identified in the systematic review. The details of the analysis given by the company are not available to the ERG in the published abstract. Please provide a more comprehensive report of the analysis.**



[redacted]

## Section C: Textual clarifications and additional points

**C1. Is there a publication date for the HLSTM01 study?**

A manuscript for study HLSTM01 has been submitted to the British Journal of Ophthalmology. If accepted, publication is expected by the end of 2016.

**C2. In Section 4.2 of the CS, the company provides reasons for the absence of randomised controlled trials (RCTs) in this patient group. Does the company consider that a plausible control group could consist of patients who receive conservative management with the removal of eye surface and application of the carrier without cells?**

Treatment with Holoclar consists in four components: (1) the initial biopsy, (2) the surgical implantation procedure (i.e. anaesthesia, pannus removal, bed preparation, product positioning, and suture), (3) the effects of Holoclar itself, and (4) the post-surgical treatment with corticosteroids and anti-inflammatory drugs. Components #1 and #2 require specific surgical procedures, which are unique for the product. Maintaining a treatment blind would therefore necessitate performing two sham surgical procedures, i.e. #1 sham biopsy and #2 pannus removal and surgical bed preparation, on the control patient, without any possible trade-off in terms of clinical benefit.

Furthermore, this approach would not be considered acceptable both ethically and clinically. Debridement of the conjunctival epithelium covering the cornea and the limbus (i.e. component #2) would generate complete exposure of the corneal surface that would be subsequently be covered by only an acellular fibrin sheet, which is characterised by its ability to be quickly reabsorbed. This would lead to vast corneal ulcerations in the postoperative phase. In this scenario, unjustified recurrence of symptoms (pain, burn and photophobia) and risk of infections are envisaged to dominate the patient's post-treatment follow-up. In addition, such a placebo arm (which is very different to the localised mechanical debridement of the conjunctival pannus used in less severe forms of LSCD) would not offer any relevant expectation for corneal epithelial restoration from the residual LSC population. The benefit-risk ratio is consequently considered not favourable for such a procedure and the comparison with the experimental treatment would generate distorted results. In addition, for ethical reasons, surgeons and/or patients would be reluctant to accept the possibility of delivering or receiving a surgical procedure in the absence of a reasonable expectation of clinical benefit and indeed in the presence of a reasonable expectation of harm.

In summary, Chiesi does not consider that a plausible control group could consist of patients who receive conservative management with the removal of the eye surface and application of the carrier without cells.

**C3. Please confirm if the first safety update report for Holoclar (due 6 months after approval by the EMA) has been submitted to the EMA.**

Chiesi confirms that the first Periodic Safety Update Report (PSUR) for Holoclar, due six months after the approval by EMA, has been submitted and approved. As Holoclar was granted a conditional marketing authorisation, PSUR submissions are required to be submitted to the EMA every six months. Chiesi therefore confirms that a second PSUR has also now been submitted and approved. Both PSURs confirmed that the benefit/risk balance for Holoclar remains unchanged.

**Enclosures**:

1. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the efficacy and safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns (HLSTM01). Protocol and Protocol Amendments, Final Version 01; 9th July 2009.

2. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency (HLSTM02). Protocol and Protocol Amendments, Final Version 01; 22nd July 2009.

3. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the safety and efficacy of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns (HLSTM04). Clinical Study Protocol, Version 1.0; 9th July 2013.

4. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the efficacy and safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns (HLSTM01). Statistical Analysis Plan, Version Final; 3rd August 2010.

5. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency (HLSTM02). Statistical Analysis Plan, Version Final; 30th August 2010.

6. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the safety and efficacy of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns (HLSTM04). Statistical Analysis Plan, Version 1.0; 30th May 2014.

7. Chiesi Farmaceutici S.p.A. Retrospective evaluation of the efficacy and safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns (HLSTM01). Case Report Form, Final Version; 13th October 2009.

8. Chiesi Limited. Data on File: Data Pack to Support Question B1. September 2016.

9. Chiesi Farmaceutici S.p.A. Holoclar Cost Effectiveness Analysis.

**Appendix G - professional organisation submission template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Professor Francisco C Figueiredo**

**Name of your organisation: Royal Victoria Infirmary & Newcastle University, Dept. of Ophthalmology, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP.**

**Are you (tick all that apply):**

**X** a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

**What is the expected place of the technology in current practice?**

The application/place of the proposed new technology is quite specific and well defined. It is to be used in patients with moderate to severe LSCD caused by chemical and thermal burns. This would be delivered by a rather small number of highly specialised eye services geographically distributed across the UK.

**How is the condition currently treated in the NHS?**

Unilateral moderate/severe LSCD caused by chemical and thermal burns are often treated in the NHS as Conjunctival Limbal Autografts (CLAU) and in case of bilateral disease as living related-Conjunctival limbal allografts (lr-CLAL) or keratolimbal allograft from cadaver donor (KLAL).

**Is there significant geographical variation in current practice?**

I believe so as this kind of operation is only performed in specialised centres around the UK.

**Are there differences of opinion between professionals as to what current practice should be?**

Possibly depending on procedure availability and previous personal experience.

**What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?**

As described above, current technology available are: CLAU, lr-CLAL and KLAL.
CLAU: (i) Advantages: easy availability and easy to perform without the need for expensive laboratory facilities. (ii) Disadvantages: Serious risk of inducing LSCD in the healthy donor eye.
lr-CLAL: (i) Advantages: Easy availability and easy to perform without the need for expensive laboratory facilities. (ii) Disadvantages: Serious risk of inducing LSCD in the healthy donor eye and high risk of rejection, combined with need to use systemic immunosuppression for a long time after the operation and serious risks associated with this treatment (e.g. infection, tumour formation, etc.).

KLAL: (i) Advantages: Easy availability and easy to perform without the need for expensive laboratory facilities. (ii) Disadvantages: Rather high risk of rejection, combined with need to use systemic immunosuppression for a long time by the recipient after the operation and serious risks associated with this treatment (e.g. infection, tumour formation, etc.).

**Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?**

Depending on the original cause of LSCD the prognosis are often different. However, the label indication for the technology is quite clear and chemical/thermal burns offers the best potential prognosis.

**Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?**

As above.

**In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?**

In my view, I would recommend specialist care services only.

**Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?**

Not necessarily. I do not believe this is a requirement.

**If the technology is already available, is there variation in how it is being used in the NHS?**

The technology has been available for a few years as part of clinical trials and NHS England IFR system.

**Is it always used within its licensed indications? If not, under what circumstances does this occur?**

As far as I am aware yes it is.

**Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.**

I am not aware of any clinical guidelines for this technology.

**The advantages and disadvantages of the technology**

**NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

The technology will be well received by the ophthalmology community in the UK once it is approved by NICE STA system. Although it is rather important to keep in mind how much it will cost the NHS and it should represent value for money to the NHS.

**If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.**

As part of the EMA conditional marketing authorisation the company is conducting a prospective, open-label, uncontrolled interventional study across Europe to assess the efficacy and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns. This trial will be instrumental to be able to demonstrate the potential benefits of the technology.

**If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.**

I certainly agree with above statement that the technology under clinical trial conditions reflects that observed in clinical practice.

**Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?**

Yes they do. The trial circumstances were similar, therefore they do reflect current UK practice.

**What, in your view, are the most important outcomes, and were they measured in the trials?**

The most important clinical outcomes in my view is complete restoration of the ocular surface integrity demonstrated clinically on slit lamp by a complete epithelised cornea with transparent cells, no superficial vessels and no delayed epithelial staining with fluorescein. This should be combined with histological confirmation of restoration of corneal phenotypic epithelial cells by corneal impression cytology (i.e. immunostaining).

**If surrogate measures of outcome were used, do they adequately predict long-term outcomes?**

The concept of a surrogate endpoint/marker is a valid concept and has been used in many clinical trials when the primary endpoint is undesirable or when the number of events is very small.

**What is the relative significance of any side effects or adverse reactions?**

Any new technology may produce unwanted or unexpected adverse reactions and side effects, therefore detection and recording of any adverse drug reactions/side effects is of vital importance so that unrecognised hazards are identified promptly and appropriate regulatory action is taken to ensure that all technologies are used safely.

**In what ways do these affect the management of the condition and the patient's quality of life?**

The proposed technology has proved to be rather safe and efficacious over the years therefore it is not expected that side effects and adverse reactions would be a problem.

**Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?**

I am not aware of any significant adverse reaction or side effect related to the proposed technology.

**Any additional sources of evidence**

**Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.**

The additional information is based on my personal experience over the last 10 years using a rather similar IMP developed locally in Newcastle that has been used in over 30 patients with total and unilateral LSCD which has proved to be very safe and efficacious treating patients with a rather similar label indication to the proposed technology under appraisal. Unfortunately, there are no randomised controlled study or national registries using similar technology. Most of the published data are case series.

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

**Implementation issues**

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

**How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?**

The availability of this technology in the NHS will be very important as there is an unmet need for such a therapy to be available. It is important to keep in mind that LSCD is a rather disabling condition resulting in blindness and ocular surface discomfort/pain with enormous impact on patient's QoL. In addition, the World Health Organisation estimates that one year with severe visual impairment is equivalent to the loss of 23 weeks of life in perfect health, If efficacious in the longer term as expected the proposed treatment will increase independence and reduce need for social and personal support (estimated to cost over £7500 per person per year.

**Would NHS staff need extra education and training?**

No. Similar operation is already practiced by a few highly specialised corneal surgeons across the UK and the after care is also well accepted and recognised in those centres.

**Would any additional resources be required (for example, facilities or equipment)?**

Not really

**Equality**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. **Please let us know if you think that this appraisal:**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

# ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]

**- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
**- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**
**- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**

**NONE OF THE ABOVE**

**Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.**

Not required as there is no equality issues related to the proposed technology.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Mr Alex J Shortt**

**Name of your organisation: Moorfields Eye Hospital NHS Foundation Trust**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify) **Clinician Scientist with 10 years experience of pre-clinical and clinical research in this field. I currently hold a Wellcome Trust Intermediate Clinical Fellowship investigating the immune reaction to transplanted stem cells.**

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**
None to declare

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**What is the expected place of the technology in current practice?**

**How is the condition currently treated in the NHS?**
Patients can be managed conservatively in which case they are treated with eye drops (steroid and antibiotic), autologous serum eye drops, and contact lenses. However this is a chronic condition and patients need life long care with frequent visits for flare ups of the condition, usually caused by infection.

In order to reconstruct the ocular surface and provide a "cure" for the condition, numerous surgical techniques have been attempted to repopulate the surface of the eye with stem cells. These can be taken from the fellow eye if it is healthy or a donor if not. Outcomes for autologous transplants are as high as 80% success at 10 years. Outcomes for allografts are much poorer. The surgical options for transplanting stem cells are: keratolimbal allograft, conjunctival limbal autograft, simple limbal epithelial transplantation and transplantation of ex-vivo cultured limbal epithelial sheets.

**Is there significant geographical variation in current practice?**
No.

**Are there differences of opinion between professionals as to what current practice should be?**
Some clinicians favour Simple Limbal Epithelial Transplantation (SLET) over ex-vivo cultured cell sheets for reasons based on access to the technology and cost.

**What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?**
The alternatives are SLET and whole tissue transplant techniques. The drawback of SLET is that the biopsies may not grow on the eye and there is no guarantee that the biopsies will contain the appropriate proportion of stem cells. The drawback of whole tissue techniques are that these require large biopsies and the procedure cannot be repeated if it fails. Also, whole tissue transplants are rapidly rejected by the immune system if they are allogeneic unless systemic immunosuppression is used.

**Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?**
Patients with very dry eyes and keratinisation of the ocular surface will not have successful outcomes because the host environment is simply too dry for engrafted cells to survive. Also, engraftment of cells into a very inflamed ocular surface is unlikely to be successful.

**In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

This treatment should only be provided in tertiary care centres. The transplant tissue has a finite shelf life and it will be essential to have an operating theatre, anaesthetist and staff ready to perform transplants at short notice

.

**If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?**

The technology has been used in research studies at several UK centres prior to it being licenced by the EMEA.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium (Nice 2007)

**The advantages and disadvantages of the technology**

**NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?**

This treatment would be a major step forward for patients because it seems to have a higher success rate due to the confirmed presence of a sufficient proportion of stem cells prior to graft release. A second major strength is the ability to repeat the procedure without undue risk to the patients fellow eye from which the biopsy is taken. Existing transplantation techniques would appear to have a lower success rate than the treatment being assessed. The logistics of sending the biopsy tissue to another facility and then having the graft shipped back when ready has practical implications in terms of co-ordination for the patient and medical staff.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Patients should have a wet eye with a Schirmer 1 test value of at least 10mm at 5 minutes. They should not have any lagophthalmos, exposure of the ocular surface or trichiasis. Inflammation should be adequately controlled.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The trial outcomes relate primarily to patients with limbal stem cell deficiency due to ocular burns. My protocol and experience of treating such patients with this technology mirrors that describes in the trials of the technology being assessed. I believe the technology being assessed would perform similarly in the UK population of patients with ocular surface burns.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Serious side effects or adverse reactions are extremely rare and are usually associated with the eye surgery itself rather than the technology being assessed. Microbial keratitis and anaesthetic complications can occur following several different corneal surgical procedures and are not specific to this technology being assessed.

**Equality and Diversity**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

**None**

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from

registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The infrastructure for treating these patients is already in place in Newcastle and Moorfields Eye Hospital London. These units have the staff and facilities required to perform these treatments and this could begin immediately following a positive recommendation. The main limitation here is the cost of the graft preparation buy the company, which would be more appropriately funded by as a specialised service by NHS England rather than Trusts seeking agreement from CCGs to recover the cost of these treatments.

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns ID899

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/148/05

Completed 12th October 2016

CONTAINS COMMERCIAL and ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

**Title:** Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns

**Produced by:** Liverpool Reviews & Implementation Group (LR*i*G)

**Authors:** Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Rachel Houten, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Ashma Krishan, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow, LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Ahmed Abdulla, Research Associate (Health Economics Modelling), LRiG, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool

Stephen Kaye, Consultant Ophthalmologist, St Paul's Eye Unit, Royal Liverpool University Hospital and Honorary Professor of Ophthalmology, Department of Eye and Vision Science, University of Liverpool

Sajjad Ahmad, Senior Clinical Lecturer, Department of Eye and Vision Science, University of Liverpool and Honorary Consultant Ophthalmologist, St Paul's Eye Unit, Royal Liverpool University Hospital

**Correspondence to:** Janette Greenhalgh, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Room 2.09, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

**Date completed:** 12th October 2016

**Source of funding:** This report was commissioned by the NIHR HTA Programme as project number 15/148/05

**Declared competing interests of the authors:** None

**Acknowledgements:** The authors would like to thank Dr Saaeha Rauz, Clinical Senior Lecturer at the University of Birmingham and Consultant Ophthalmologist at the Birmingham and Midland Eye Centre who provided feedback on the draft version of the report.

**Rider on responsibility for report:** The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows:** Greenhalgh J, Mahon J, Houten R, Krishan A, Boland A, Kotas E, Dundar Y, Beale S, Abdulla A, McEntee J, Kaye SB, Ahmad S. Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2016.

## Contributions of authors:

| | |
|---|---|
| Janette Greenhalgh | Project lead, drafted clinical results section and supervised the final report |
| James Mahon | Critical appraisal of the company economic model and proposal of alternative interpretations of the economic evidence |
| Rachel Houten | Summary and critical appraisal of economic evidence. Checking and validation of the economic model and critique |
| Ashma Krishan | Critical appraisal of the statistical evidence, drafted clinical results section |
| Angela Boland | Critical appraisal of the clinical and economic evidence |
| Eleanor Kotas | Critical appraisal of the company database searching |
| Yenal Dundar | Critical appraisal of the clinical section of the company submission |
| Sophie Beale | Summary of the company economic evidence |
| Ahmed Abdulla | Checking and validation of the economic model and critique |
| Joanne McEntee | Critical appraisal of the company submission |
| Stephen Kaye | Clinical advice and critical appraisal of the clinical sections of the company submission |
| Sajjad Ahmad | Clinical advice and critical appraisal of the clinical sections of the company submission |

All authors read and commented on draft versions of the ERG report.

**Table of contents**

**List of tables**

**List of figures**

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ACLSCT | autologous cultured limbal stem cell transplantation |
| AMT | amniotic membrane transplantation |
| BSC | best supportive care |
| BSE | best seeing eye |
| CD | cadaveric donor |
| CI | confidence interval |
| CLAL | conjunctive limbal allograft from a living relative or cadaveric donor |
| CLAU | conjunctival limbal autograft |
| CS | company submission |
| CSR | clinical study report |
| DALK | deep anterior lamellar keratoplasty |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EQ-5D | EuroQol-5 dimension |
| ERG | Evidence Review Group |
| HLSTM | case series studies providing the clinical data for Holoclar |
| HRQoL | health-related quality of life |
| ICER | incremental cost effectiveness ratio |
| ITT | intention to treat |
| KLAL | keratolimbal autograft |
| Lr-CLAL | conjunctival limbal allograft from a living related donor |
| LSCD | limbal stem cell deficiency |
| LSCT | limbal stem cell transplantation |
| LY | life year |
| NICE | National Institute for Health and Care Excellence |
| OS | ocular surface |
| PAS | Patient Access Scheme |
| PKP | penetrating keratoplasty |
| QALY | quality adjusted life year |
| RCT | randomised controlled trial |
| SA | sensitivity analysis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SLET | simple limbal epithelial transplantation |
| STA | single technology appraisal |
| SmPC | summary of product characteristics |
| TRAE | treatment-related adverse event |
| UCVA | uncorrected visual acuity |
| VA | visual acuity |
| WSE | worst seeing eye |

# 1 SUMMARY

## *1.1 Scope of the submission*

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE by Chiesi UK Ltd to support the use of a specific type of ex vivo expanded autologous human corneal epithelial cells, Holoclar®, within the licensed marketing authorisation for the treatment of moderate to severe limbal stem cell deficiency (LSCD) due to ocular burns. For brevity, throughout this ERG report, the intervention is referred to as 'Holoclar'.

Holoclar has been licensed in Europe since February 2015 for the treatment of adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity [VA]), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2mm$^2$ of undamaged limbus is required for biopsy. The marketing authorisation is conditional on the company providing the results of an on-going prospective, European, uncontrolled phase IV study known as HLSTM03 (or HOLOCORE). The company expects the study results to be available in 2020.

The main clinical evidence presented in the company submission (CS) comes from the HLSTM01 study, an unpublished, retrospective case series study of 104 patients who were treated with Holoclar in two Italian ophthalmology centres between 1998 and 2008.

## *1.2 Critique of the decision problem in the company submission*

**Intervention**

The intervention discussed in the CS is Holoclar. Treatment with Holoclar requires cells to be taken from a biopsy of the patient's undamaged limbus and shipped from the treating hospital to the site of Holoclar manufacture (Italy) where the cells are cultured on a fibrin membrane and then frozen. When the date for surgery is set, the manufacturer ships Holoclar to the hospital where it is implanted in the patient's eye. The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium.

Holoclar is a living tissue equivalent and consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm$^2$), including on average 3.5% (0.4 to 10%) limbal stem cells, and stem cell-derived transient amplifying and terminally differentiated cells, attached on a supportive 2.2cm diameter fibrin layer and maintained in the transport medium. Each sheet of product is sufficient for a single treatment. Holoclar is the first advanced therapy medicinal product (ATMP) containing stem cells to receive a Marketing Authorisation in Europe.

**Population**

The population described in the final scope issued by NICE is adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2mm$^2$ of undamaged limbus. This is the same as the population described in the conditional licence for Holoclar issued by the European Medicines Agency (EMA).

The key clinical evidence describing treatment with Holoclar presented in the CS is derived from a single case series study (HLSTM01). Only one of the patients included in the HLSTM01 case series study had both eyes treated with Holoclar.

The company estimates that a maximum of 121 patients are likely to be currently eligible for treatment with Holoclar in the NHS in England. In addition to the prevalent population, there are likely to be 13 patients every year who are eligible for treatment with Holoclar.

**Comparators**

In the final scope issued by NICE, for patients with **unilateral** LSCD, the comparators are listed as conjunctival limbal autograft and BSC only. Clinical advice to the ERG is that limbal epithelial stem cells allografts are also used in the UK to treat unilateral LSCD.

In the final scope issued by NICE, for people with **bilateral** LSCD, the comparators are conjunctival limbal autograft, limbal epithelial stem cell allografts and BSC. Clinical advice to the company and to the ERG is that in the UK, conjunctival limbal autograft is unlikely to be used to treat patients with bilateral LSCD.

The ERG agrees with the company that the available evidence describing the clinical effectiveness of the comparators should be viewed with considerable caution.

The ERG is aware of emerging transplant techniques that are currently being trialled in different treatment centres in the UK and in other countries to treat patients with moderate to severe LSCD due to ocular burns (e.g., simple limbal epithelial transplant [SLET]).

**Outcomes**

Clinical evidence for the efficacy of Holoclar is reported in the CS for the majority of the outcomes specified in the final scope issued by NICE: clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation, symptoms of LSCD including pain, burning and photophobia, VA and adverse effects (AEs) of treatment. The outcomes from the HLSTM01 case series study are reported post-operatively at 12 months for all patients; for a small group of patients later data are also available. Health-related quality of life (HRQoL) data pertaining to Holoclar are not presented in the clinical effectiveness section of the CS.

**Other considerations**

According to the economic analysis section of the final scope issued by NICE, the cost effectiveness analysis should include consideration of the benefit in the best seeing and worst seeing eyes.

In the company's unilateral LSCD model, by definition, the worst seeing eye is treated. In the company's bilateral LSCD model, by definition, both eyes are treated.

### 1.2.1 Equality and End of Life considerations

It is the company's opinion that, if Holoclar were not made available in the NHS in England, then a significant equality issue would arise for patients with LSCD due to ocular burns that were incurred whilst serving in the armed forces. The company highlights that these patients are likely to also have experienced the loss of limbs or other life changing events or injuries, both physical and mental, over and above those experienced by the general population of patients with the same condition. The ERG does not consider this to be an equality or equity issue.

The company has not presented a case for Holoclar to be assessed against the NICE End of Life criteria.

## *1.3 Summary of the submitted clinical effectiveness evidence*

The company did not identify any randomised controlled trials (RCTs) comparing Holoclar with any treatment in patients with moderate to severe LSCD due to ocular burns. Consequently, the company presents the results of a case series study (HLSTM01); this study includes a substantial number of patients (n=104) with a rare disease. Supportive evidence is also provided from two other case series studies known as HLSTM02 (n=29) and HLSTM04 (n=15). None of these studies are published.

In the intention-to-treat (ITT) population of the HLSTM01 case series study, transplant success (defined as: composite endpoint of rate of patients with none or mild superficial corneal neovascularisation and none or trace epithelial defects) was reported in 75 cases (72.1%; 95% confidence interval [CI]: 62.5% to 80.5%). Results of the sensitivity analysis excluding missing data were similar (75.8%; 95% CI: 66.1% to 83.8%). A masked independent assessor evaluated the data that were available for each case at baseline and at 12 months (n=46); the results suggested that the treatment was a success in 31 out of 46 cases (67.4%).

Visual acuity (measured using the Snellen chart) was improved by at least one line in 49% of patients (95% CI: 39.4% to 58.6%) and in 83.3% of patients (95% CI: 66.1 to 100%) without stromal scarring (15/18). The number of patients with symptoms of LSCD (pain, blurring, and photophobia) decreased between baseline and 12 months post-surgery.

There were six serious AEs reported (three were fatal) after six transplantations (5.3%). None were considered to be treatment-related. After 19 transplantations, 22 adverse drug reactions (16.8%) were reported. Adverse events that may have been related to corticosteroid treatment included five cases of glaucoma and one case of gastritis. One case of glaucoma was considered by the company to be treatment-related.

The company's systematic review of evidence from comparator studies identified one randomised study of 20 patients with unilateral LSCD who were treated with conjunctival limbal autograft sourced from either a living relative or derived from a cadaver. The remaining studies identified were either case studies or case series studies. The company stated that it was inappropriate to pool data from any of the identified comparator studies and instead provided a narrative summary of the data described in the comparator studies.

## *1.4 Summary of the ERG's critique of the submitted clinical effectiveness evidence*

The company carried out a search to identify evidence for the clinical effectiveness of Holoclar and a search to identify evidence for the clinical effectiveness of comparator technologies. The ERG is satisfied with the company's search strategies and is not aware of any studies that should have been included in the systematic reviews.

The company did not identify any RCTs that compare the use of Holoclar with any other treatment. Instead, the company presents the results of a retrospective case series study with a descriptive, observational design (HLSTM01). Using data from the HLSTM01 case series study, the company reports p-values and performs hypothesis testing. The ERG considers that this approach to data analysis is inappropriate as the purpose of a case series study is only to describe data.

The ERG agrees that the company has made attempts to mitigate against potential biases in the HLSTM01 case series study e.g., by using a pre-specified protocol to select cases, partially blinding outcomes and by quantifying the number of missing patient cases and assessing the impact of missing data. Despite these attempts, the ERG considers the HLSTM01 to be a poor quality case series study.

The marketing authorisation for Holoclar issued by the EMA includes its use in patients with unilateral and bilateral LSCD. There is no clinical effectiveness evidence presented in the CS to support the use of Holoclar to treat both eyes in patients with moderate to severe LSCD.

The ERG agrees with the company that pooling of data from the comparator studies is not possible inappropriate due to high levels of parameter heterogeneity.

## *1.5 Summary of submitted cost effectiveness evidence*

The company developed two de novo economic models in Microsoft Excel to compare the cost effectiveness of a unilateral or bilateral Holoclar transplant with four comparators, conjunctival limbal autograft (CLAU), conjunctival limbal allograft from a living relative (Lr-CLAL), keratolimbal autograft (KLAL) and best supportive care (BSC). The models have two main structural elements; a decision tree component for the initial treatment that includes any biopsy and transplant attempts, and a Markov component to capture longer-term outcomes. There are five health states represented in the Markov element of the model; the first two are relevant for the first year post-transplant and represent whether treatment has been successful or has failed. Beyond the first year post-transplant, patients can either be in a stable health state, have a failed transplant and be managed by BSC or die of other causes. Both models follow the same structure with the addition of treatment of the second eye in the bilateral case and there is a 12-month delay between the transplants in each eye. The model time horizon is set at 50 years with annual cycles in the Markov element. The model perspective is that of the UK NHS. Outcomes are measured in quality adjusted life years (QALYs). Costs and utilities are discounted at an annual rate of 1.5%. Utility values are obtained from both a bespoke standard gamble stated preference exercise and a literature search. Resource use and costs are estimated based on information from the HLSTM01 case series study for Holoclar and the expected patient pathways for the comparators.

In the base case for unilateral disease, Holoclar is dominated by CLAU as it is less effective and more expensive; the opposite is true for the comparison with BSC, therefore Holoclar dominates BSC. Holoclar provides additional benefit over Lr-CLAL (+2.36 QALYs) at an increased cost of £16,988. The company's base case incremental cost effectiveness ratio (ICER) for Holoclar versus Lr-CLAL is £7,185 per QALY gained. Holoclar is also more effective

than KLAL (+2.29 QALYs) at an additional cost of £5,167, resulting in an ICER of £2,255 per QALY gained.

In the base case, for bilateral disease, Holoclar is dominated by CLAU and dominates BSC. Holoclar provides additional benefit over Lr-CLAL (+2.89 QALYs) at an increased cost of £35,986. The company's base case ICER for Holoclar versus Lr-CLAL is £12,438 per QALY gained. Holoclar is also more effective than KLAL (+2.69 QALYs) at an additional cost of £17,572, resulting in an ICER of £6,533 per QALY gained.

The company carried out a number of alternative scenario analyses for patients with unilateral and bilateral disease.

**Scenario analysis: unilateral disease**

Holoclar is dominated by CLAU for all scenarios except when the source of clinical evidence for CLAU is changed and either the utility decrement for disfigurement is removed (ICER=£488,615 per QALY gained) or the time horizon is restricted to 22 years (ICER=£167,201 per QALY gained). When the time horizon is restricted to 22 years and there is a change to the source of the KLAL transition probabilities, the size of the ICER per QALY gained for Holoclar versus KLAL increases (+£27,233); for Holoclar versus BSC, Holoclar no longer dominates BSC with an ICER of £5,743 per QALY gained. Removal of the disfigurement utility decrement has a big influence on the comparison of Holoclar versus Lr-CLAL for patients with unilateral disease as the ICER is increased by £27,891 per QALY gained. When the discount rate is increased from 1.5% to 3.5%, Holoclar no longer dominates BSC (ICER=£3,563 per QALY gained); similarly, the ICERs increase for Holoclar versus Lr-CLAL (£13,997 per QALY gained) and versus KLAL (£12,990 per QALY gained).

**Scenario analysis: bilateral disease**

When the sources used for the transition probabilities are changed for comparative interventions and the disfigurement utility decrement is removed, Holoclar is no longer dominated by CLAU (ICER=£486,145 per QALY gained). In this same scenario, for Holoclar versus Lr-CLAL, the ICER is decreased by £10,510 per QALY gained and increased for Holoclar versus KLAL (+£12,416 per QALY gained), and Holoclar continues to dominate BSC. Increasing the annual discount rate from 1.5% to 3.5% has the biggest impact on the comparison of Holoclar with Lr-CLAL (ICER=£34,817 per QALY gained) and BSC, which Holoclar no longer dominates (ICER=£6,708 per QALY gained).

## 1.6 Summary of the ERG's critique of cost effectiveness evidence

The ERG is satisfied with the company's systematic review of cost effectiveness evidence and considers that the submitted models were reasonably well constructed with no flaws in the algorithms used to generate base case results.

The company's clinical effectiveness estimate for Holoclar is derived from a single, retrospective, case series study. Despite the study investigators' attempts to mitigate bias, the study has methodological flaws. Furthermore, the effectiveness evidence for each of the comparators that are used in the economic models is based on pooled data from the company's systematic review of the literature. The ERG notes that this approach is not described in the clinical or economic sections of the CS; in the clinical section of the CS, the company stated that pooling the data was not appropriate due to significant parameter heterogeneity between studies. Consequently, whether robust methods have been used to pool the data is unknown. However, as the individual studies have very small sample sizes, the ERG considers it doubtful that selection of any one study will produce more robust results than the pooled analysis. The ERG considers that the weak evidence base from which the intervention and comparator effectiveness is drawn needs to be taken into account when assessing the robustness of the ICERs generated by the company models.

In addition, the ERG has some concerns about the comparators employed in the economic models. First, the ERG considers that, in line with the NICE scope, CLAU is a treatment option for patients with unilateral disease and should be considered in the same way as the other comparators. The company claims that there are patients who are unsuitable for CLAU and/or who are unwilling to undergo treatment with CLAU and/or who have had an unsuccessful CLAU transplant. Clinical advice to the ERG is that this subgroup of patients is not clinically recognised or sufficiently well established and that CLAU is a valid treatment option for patients with moderate to severe LSCD.

Second, for patients with bilateral disease who are considering treatment in both eyes, the ERG agrees with the company that CLAU is not a valid treatment option and should not be considered alongside the other comparators.

However, the company does not present clinical effectiveness evidence to support the use of Holoclar to treat both eyes or to support the assumption that treatment of the second eye is is as effective as treatment in the first eye. The ERG considers this assumption to be implausible. For example, for patients with bilateral disease, any repeat biopsies that are necessary (which can be up to six in total) would have to be taken from a damaged eye. The company does not provide sufficient detail regarding whether or not this is possible in clinical practice. As such,

the cost effectiveness results associated with bilateral treatment cannot be used to inform treatment decisions for this group of patients.

Furthermore, the ERG considers that there are four issues that have a major impact on the cost effectiveness results generated by the company model (i.e., HRQoL, the discount rate, the use of autologous serum eye drops and use of KLAL on failure with Lr-CLAL).

The ERG agrees with the company that there are no HRQoL data available for this group of patients; the company has not collected any HRQOL data and there no published HRQoL data available from other relevant studies. After consultation with clinical experts and reviewing the utility values used in other studies of eye related diseases, the ERG considers that the utility values associated with the different health states employed in the base case are implausibly low and suggests using higher values.

The ERG considers that the stipulated NICE criteria permitting the application of a 1.5% discount rate for costs and benefits have not been met as Holoclar does not extend life or affect a cure for terminal disease. In addition, there is considerable uncertainty surrounding the size of the HRQoL impairment of patients with LSCD and the ability of Holoclar to restore these patients to full health. The ERG therefore considers that the standard 3.5% discount rate for costs and benefits should be used.

The cost of autologous serum eye drops is the main driver of cost in the economic models for Holoclar versus Lr-CLAL, KLAL and BSC.

The ERG's clinical experts consider that if autologous serum eye drops are used post-operatively, then they will be used after all transplantations including Holoclar. In the base case, it is assumed that these eye drops are not used after treatment with Holoclar but are used after all other transplantations. The ERG has therefore modified this assumption in the models and assumed that autologous serum eye drops are included in the cost of Holoclar treatment. Given the comparative nature of cost effectiveness analysis, the addition of autologous serum eye drops to treatment with Holoclar or removal from the comparator interventions has the same effect.

Whether autologous serum eye drops are routinely used to treat patients with flare-ups in the NHS is unknown. In the models, the company assumes that two flare-ups per year are treated with autologous serum eye drops. For clarity, the ERG considers that the cost effectiveness results associated with a scenario that does not permit the routine use of autologous serum eye drops for flare-ups must also be presented.

The company assumes that patients only have one type of transplant which is a particular issue for Lr-CLAL where it is assumed a patient can only have one transplant in their lifetime.

The ERG considers this assumption to be particularly implausible. When Lr-CLAL fails either the relative who offered a first donation could offer a second or a cadaver donor could be used to enable the transplant procedure to be repeated. The ERG presents a scenario, for unilateral patients, where two attempts at Lr-CLAL can occur. Given the similarities in terms of costs and effectiveness of Lr-CLAL and KLAL, this scenario can represent either two donations from a living donor or a second transplant from a cadaver donor.

## *1.7 Summary of company's case for End of Life criteria being met*

The company has not presented a case for treatment with Holoclar to be considered under NICE's End of Life criteria.

## *1.8 ERG commentary on the robustness of evidence submitted by the company*

### 1.8.1 Strengths

**Clinical evidence**

- Good quality systematic reviews were conducted in a complex disease area
- 104 patients with a rare disease were included in the HLMST01 case series study
- The company has a record of the total number of patients treated with Holoclar and is confident that there is more clinical effectiveness data to support the use of Holoclar than is available for any of the individual comparators.

**Cost effectiveness evidence**

- The economic models were reasonably well constructed
- Where data were limited, the company went to great lengths to identify data that could be used in the economic models
- The company carried out a comprehensive range of deterministic sensitivity analysis and scenario analyses.

### 1.8.2 Weaknesses and areas of uncertainty

**Clinical evidence**

- The evidence used to support the clinical effectiveness of Holoclar is derived primarily from a retrospective, single, case series study. The study authors have attempted to mitigate bias, but methodological flaws remain
- There is no clinical effectiveness evidence presented in the CS to support using Holoclar to treat two eyes in patients with bilateral LSCD
- The data available for the clinical effectiveness of the comparator technologies are weak. The majority of studies are small and observational in design.

**Cost effectiveness evidence**

- There is no gold standard comparator to which Holoclar can be compared
- For patients with unilateral disease, the company's base case ICER demonstrates that Holoclar is not cost effective compared to CLAU
- The company does not present any clinical effectiveness evidence to support the use of Holoclar to treat both eyes in patients with bilateral LSCD. Therefore, the ERG does not consider the cost effectiveness results associated with the company's bilateral model to be informative.

## *1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG*

The ERG identified several fundamental issues that cast doubt on the cost effectiveness of Holoclar versus all comparators. The ERG applied changes to the company models to address the identified issues including:

- Using a more plausible utility decrement for disfigurement and alternative utility values for differing VA
- Applying a 3.5% annual discount rate for costs and benefits
- Using autologous serum eye drops post-operatively for all procedures
- Not using autologous serum eye drops for flare-ups
- Allowing a second transplant attempt following the failure of treatment with Lr-CLAL.

**Results in the unilateral model**

CLAU dominates Holoclar when all of the ERG's modifications are implemented (individually and in combination). For Holoclar versus Lr-CLAL, with two transplant attempts, the ICER is £152,590 per QALY gained (£179,066 in the no serum eye drops at flare-up scenario). For Holoclar versus KLAL, the ICER is £33,473 per QALY gained (£60,996 in the no serum eye drops at flare-up scenario). For Holoclar versus BSC, the ICER is £8,155 per QALY gained (£35,489 in the no serum eye drops at flare-up scenario).

**Results in the bilateral model**

Application of the ERG's changes to utility values, discount rate and modifications to the use of autologous serum eye drops resulted in ICERs for Holoclar versus Lr-CLAL of £67,219 per QALY gained (£111,654 in the no serum eye drops at flare-up scenario). For Holoclar versus KLAL, the ICER is £75,457 per QALY gained (£122,468 in the no serum eye drops at flare-up scenario). For Holoclar versus BSC, the ICER is £14,288 per QALY gained (£50,973 in the no serum eye drops at flare-up scenario). However, the ERG considers that the ICERs generated by the bilateral LSCD model are of limited value due to i) the lack of evidence for the clinical

effectiveness of Holoclar to treat two eyes in the same patient and ii) the clinical implausibility of the company's assumption that Holoclar would be as effective in the second eye as in the first eye.

# 2 BACKGROUND

## *2.1 Critique of company's description of underlying health problem*

Section 3.1 of the company submission (CS)[1] includes an overview of limbal stem cell deficiency (LSCD). Section 3.2 provides a description of the effect of moderate to severe LSCD due to ocular burns on patients, carers and society. Section 4.4 discusses the impact of vision on life expectancy. Key points from these sections are included as bulleted items in Box 1. The ERG considers that these points appropriately summarise the underlying health problems.

Box 1 Company overview of limbal stem cell deficiency

**Aetiology of moderate to severe LSCD**

- LSCD is characterised by a loss or deficiency of the progenitor stem cells located in the limbus that are vital for re-population of the corneal epithelium and to the barrier function of the limbus. This results in epithelial breakdown and recurrent or persistent epithelial defects, conjunctivalisation of the corneal surface with neovascularisation, chronic inflammation and corneal scarring. All of these contribute to loss of corneal transparency, potential visual loss, chronic pain and burning, photophobia and keratoplasty failure. In severe LSCD, part of the cornea, usually including the pupillary area, is covered by a thick fibrovascular pannus.[2] LSCD is an important cause of corneal blindness.[3]

- LCSD may result from direct injury to the limbal stem cells, destruction of the limbal stem cell niche, or both.[4] It can be caused by a wide variety of primary (inherited) and secondary (external) causes.[5-8] More rarely, there are unknown causes.[6,9]

- Secondary causes of LSCD often arise as a result of direct damage to the limbal stem cells.[6] This is most frequently associated with the sequelae of thermal (sometimes referred to as physical) or chemical (acid or alkali) burns and may also arise as a result of direct instilled drugs, contact lens usage or some therapies.[6] For example, prolonged use of high dose topical mitomycin C application may be associated with a relatively high incidence of LSCD.[10]

**Epidemiology of moderate to severe LSCD**

- LSCD is most frequently seen associated with severe physical or chemical burns[4,6,7] and bilateral involvement (both eyes) is reported to affect 20-38% of patients presenting with chemical burns.[11,12] Chemical burns are typically caused by acid or alkali injury[7,11] with household cleaners containing sodium hydroxide being among the most common causes of alkali injury. Acidic injuries are less common than alkali injuries and typically cause less damage to the ocular surface.[7]

- The estimated prevalence of LSCD due to ocular burns in Europe is 0.3 per 10,000 people.[13] In the UK, the reported incidence of LSCD due to severe chemical corneal injury is 0.02 per 100,000 in patients who had a mean age at time of injury of 33.8 years (median 38.5 years, range 10-59 years).[14]

- A 2011 review of 28 case reports and series published over 13 years[15] examined data from 583 patients (597 eyes) from centres undertaking cultured limbal stem cell transplantation in Australia, Germany, India, Iran, Italy, Japan, Taiwan, UK, and USA. In the studies reviewed, 75% of LSCD cases were caused by physical or chemical burns. In addition, the majority of patients were young males, who were treated for burns. A 2015 study of 16 patients[16] also documented chemical burns (31%) as being the most common cause of LSCD.

- Chronic effects on the ocular system have been documented in people exposed to sulphur mustard, (a chemical warfare agent) during the Iran-Iraq war, with an incidence of approximately

1%.[17] It is not clear whether LSCD is a direct effect of sulphur mustard toxicity or whether LSCD gradually progresses to a severe form because of chronic inflammation.[17]

**Course of moderate to severe LSCD**

- LSCD is a severe and painful condition that can affect patients with varying degrees of extent and severity.[5,16] It can be unilateral or bilateral (affecting one eye or both eyes) and either partial or total (affecting part or all of the cornea).[5,16]

- Although partial LSCD may be limited to a few sectors of the cornea, central vision can still be compromised.[8] If the problem is bilateral, the patient may be effectively blind. Corneal blindness affects quality of life and is often associated with an increased economic burden.[3]

- In terms of health consequences for patients with LSCD, the associated ocular surface disease poses a difficult management problem.[18] The clinical signs of LSCD are conjunctivalisation of the cornea with associated goblet cells, intense vascularisation, chronic inflammation, recurrent epithelial defects and stromal scarring.[5] Intense inflammation can cause secondary problems like increased eye pressure, the development of glaucoma and death of the optic nerve ganglion cells.[3]

- From the patient's perspective, the eye has little or no vision, it is often cosmetically unsatisfactory, and it may be uncomfortable or painful.[9,18,19] The symptoms experienced include excessive pain, eye discomfort associated with ocular surface problems including severe irritation, discomfort, photophobia, tearing, blepharospasm, chronic inflammation and redness, and decreased vision.[9,19] Most patients will lose their vision during the course of the disease.

**Effects on patients, carers, families and society**

- Patients with moderate to severe LSCD and their families face serious social challenges. Directly and indirectly, visual impairment interferes with many daily activities. In the case of adults, the possibilities for gainful employment are severely limited due to being unable to meet the greater visual demands in work situations, as is their participation in many other activities. To this is often added a loss of social status and self-esteem. The physical limitations and psychosocial implications of visual impairment cannot be measured in exact monetary terms. Nevertheless, it is clear that they diminish the quality of life not only for visually impaired persons, but for their families as well.[20]

- The effect of LSCD on patients is further exemplified by patient testimonial. Two testimonials have been provided by patients matching the indication for Holoclar and who were treated with limbal stem cell transplantation. (CS, p55 to 56).

**Impact on life expectancy**

- Given the estimated prevalence of LSCD due to ocular burns (0.3 per 10,000 people in Europe)[13] there are no data examining the effects of this condition on life expectancy. However, regional and global average life expectancies and health life expectancy at birth for 2015 have been reported by the WHO.[20]

LSCD=limbal stem cell deficiency; WHO=World Health Organisation
Source: CS, Sections 3.1, 3.2 and 4.4

## *2.2 Summary and critique of the company's overview of current service provision*

### 2.2.1 Current management options

In Section 3.1.4 of the CS, the company discusses the current management options for patients with moderate to severe LSCD due to ocular burns. The options include supportive management, conservative surgical options and invasive surgical techniques. The company explains that the aim of treatment is to restore the ocular surface and achieve corneal clarity.

The ERG considers that the discussion provided by the company is detailed and comprehensive. The company provides a helpful table that summarises the management options discussed in Section 3.1.4 of the CS (see Table 1).

Table 1 Current management options for LSCD

| Supportive treatments | Conservative surgery | Limbal stem cell transplantation | |
|---|---|---|---|
| | | **Procedure** | **Features** |
| Autologous serum drops<br><br>Eye lubrication<br><br>Therapeutic soft contact lens<br><br>Therapeutic scleral lens | Corneal scraping<br><br>Amniotic membrane transplantation (AMT) | CLAU: conjunctival limbal autograft | • Autograft from a patient's healthy eye<br>• Unsuitable for bilateral LSCD<br>• Minimum 4-6mm$^2$ of limbal tissue superiorly and inferiorly (minimum 8-12mm$^2$ total) is dissected from the patients other healthy eye and transplanted using a conjunctiva carrier[21-23]<br>• No immunosuppression required<br>• Risk of inducing LSCD in donor eye[6,22] |
| | | CLAL: conjunctive limbal allograft from a living relative (Lr-CLAL) or cadaveric donor | • Allograft from living relative or cadaveric donor.<br>• Suitable for bilateral LSCD<br>• Minimum 4-6mm$^2$ of limbal tissue superiorly and inferiorly (minimum 8-12mm$^2$ total) is dissected from the donor eye and transplanted using a conjunctiva carrier<br>• Requires systemic immunosuppression[24]<br>• Risk of disease transmission and neoplasia[6]<br>• Risk of inducing LSCD in the donor eye[6,22] |
| | | KLAL: keratolimbal allograft | • Allograft from cadaveric donor<br>• Suitable for bilateral LSCD[25,26]<br>• Entire donor limbus can be transplanted using the cornea as carrier tissue[9]<br>• Requires systemic immunosuppression[24]<br>• Risk of disease transmission and neoplasia[6] |

AMT=amniotic membrane transplantation; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; LSCD=limbal stem cell deficiency
Source: CS, Table 9

The company explains that **supportive management** includes ocular surface lubrication to prevent epithelial adhesion to the tarsal conjunctiva and to reduce shear stress.

**Conservative surgical options** include corneal scraping and amniotic membrane transplantation (AMT). The aim of corneal scraping is to remove overgrown conjunctiva and allow corneal healing and encourage repopulation of corneal epithelial stem cells. More than one procedure may be needed as the conjunctival epithelium migrates more rapidly than the corneal epithelium.[6]

The role of AMT is to encourage the production and migration of any remaining limbal epithelial stem cells and to reduce inflammatory reactions.[27] The amniotic membrane supports the growth of a healthy epithelium and the recovery of the corneal surface, thereby improving visual acuity (VA) and reducing pain and photophobia.[6] The AMT procedure may be used after corneal scraping[6] or as an adjunct to limbal stem cell transplantation.[25,27-29] The company reports that the biological source of the membrane may have an impact on clinical outcomes[6]

and that there is a theoretical risk of disease transmission (hence serological screening is carried out prior to transplantation).[19]

**Invasive surgical procedures** encompass three limbal stem cell transplantation techniques: conjunctival limbal autograft (CLAU), conjunctive limbal allograft from a living relative or cadaveric donor (CLAL) and keratolimbal allograft (KLAL). The differences between the three transplant techniques are related to the source of the donor stem cells and the carrier tissue used to transfer stem cells (Table 1). The final treatment decision takes into account a number of factors, such as the extent of the LCSD (bilateral or unilateral), patient expectation and willingness to undergo the procedure, the risk to the healthy eye and the availability and willingness of a living related donor.

Adjunctive surgical procedures might be carried out with limbal stem cell transplantation procedures, for example, penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK), with or without cataract surgery.[25] Both PKP (a full-thickness corneal graft) and DALK (selective replacement of the anterior layer of the cornea that leaves an intact endothelium) are used as treatments for corneal stromal scarring.

The company points out (CS, p53) that the success of the transplantation procedure is dependent on the condition of the ocular surface and its environment. The ERG understands that patients may need to undergo procedures prior to transplantation surgery, including (but not limited to) eyelid reconstruction, management of glaucoma, management of inflammation, corneal replacement. The eye must be 'quiet' for at least 3 months prior to transplantation surgery.

### 2.2.2 Holoclar and its proposed place of treatment in the NHS

Holoclar is a living tissue equivalent and consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm$^2$), including on average 3.5% (0.4 to 10%) limbal stem cells, and stem cell-derived transient amplifying and terminally differentiated cells, attached on a supportive 2.2cm diameter fibrin layer and maintained in the transport medium.[30] Each sheet of product is sufficient for a single treatment.[30]

Holoclar is a non-standard type of CLAU. Other non-standard types of CLAU include 'Simple Limbal Epithelial Treatment' (SLET). Treatment with Holoclar requires cells to be taken from a biopsy of the patient's limbus and shipped from the treating hospital to the site of Holoclar manufacture (Italy) where the cells are cultured on a fibrin membrane and then frozen. The manufacturer must receive the cells taken during the biopsy within 24 hours of acquisition from the patient. When the date for surgery is set, the manufacturer ships Holoclar to the hospital

where it is implanted in the patient's eye. Transplantation must take place within 36 hours of Holoclar being despatched by the manufacturer to the hospital.

The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium. Holoclar is the first advanced therapy medicinal product (ATMP) containing stem cells to receive a Marketing Authorisation in Europe.

The company states (CS, p36) that in the UK, treatment with Holoclar will be carried out in two specialist ophthalmology centres (one in London and one in Newcastle). The company explains that limiting the number of treatment centres will ensure that the requisite surgical skills and experience in the treatment of the rare condition of LSCD will be developed and maintained. The company also states that Holoclar is to be commissioned by NHS England specialised services

The company states (CS, p58 and p59) that the introduction of Holoclar will not change the current treatment pathway within the NHS and considers Holoclar to be an alternative treatment option for the groups of patients listed in Table 2. The ERG notes that the European Medicines Agency (EMA) marketing authorisation[13] for Holoclar specifies its use in patients with moderate to severe LSCD due to ocular burns; there is no specific reference to Holoclar use in unilateral LSCD or bilateral LSCD.

Table 2 Patients with moderate to severe LSCD who would be treated with Holoclar

| **Patient subgroup** | |
|---|---|
| **Unilateral LSCD** | **Bilateral LSCD**<br>(Minimum of 1-2mm$^2$ of undamaged limbus) |
| Patients who are unsuitable for treatment with CLAU or who are unwilling to undergo CLAU because of concerns about damage to their donor eye | As an alternative to Lr-CLAL in patients without an available and/or willing live-related donor |
| Failed treatment with CLAU (once-only treatment) | Patients who are unsuitable for topical and systemic immunosuppression (immunosuppressive treatment is mandatory following Lr-CLAL and KLAL transplantation) |
| | Patients who require a successful treatment outcome beyond 3 to 5 years |

CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; Lr-CLAL= CLAL from a live related donor; LSCD=limbal stem cell deficiency
Source: CS, p58

The ERG notes from Table 2 that the company is suggesting that for bilateral LSCD, the duration of successful treatment with conjunctival limbal allograft form a living relative (Lr-CLAL) and KLAL is between 3 and 5 years. Clinical advice to the ERG is that treatment

success varies between studies and also varies according to the use of immunosuppression treatment and the baseline characteristics of the patients.

### 2.2.3 NICE guidelines and NHS England policies

Section 3.5 of the CS describes the place of Holoclar in relation to NICE guidelines (Table 3), the NICE pathway for eye conditions (Table 3), the NHS Outcomes Framework and NHS England policies (Table 4). The ERG considers that the information provided by the company is appropriate and comprehensive.

Table 3 Company comments on the place of Holoclar within NICE guidelines and the NICE pathway

| NICE guideline | Summary of guideline | Company comments |
|---|---|---|
| IPG304[31] (2009) Corneal endothelial transplantation | Supports the use of corneal endothelial transplantation (the replacement of diseased corneal endothelium with a cadaveric donor endothelial graft) in patients with endothelial dysfunction. | For some patients with unilateral and partial bilateral LSCD, Holoclar would provide an alternative treatment option to corneal endothelial transplantation. |
| IPG216[31] (2007) Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium.* | The evidence for the safety and efficacy of tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium was not adequate for this procedure to be used without special arrangements for consent and for audit or research. Clinicians who wish to use the procedure should inform the clinical governance leads in their trust, ensure that patients understand the uncertainty about safety and efficacy, audit and review clinical outcomes of all patients undergoing the procedure. | Holoclar would provide a 'preferred' treatment alternative to tissue-cultured limbal stem cell allograft transplant for regrowth corneal epithelium for patients with moderate to severe LSCD. |
| NICE Pathway for Eye Conditions[32] | Describes the treatment pathway for patients with eye conditions. | The appropriate place for Holoclar within the NICE treatment pathway is in the Front of the eye' section in 'other corneal disease'. The NICE pathway for eye conditions is not well defined and that the majority of surgical treatments in use in the NHS have not been appraised by NICE. The introduction of Holoclar into the NHS would provide clear guidance in this area of the pathway. |

*IPG216 was considered for reassessment in 2010 but was not updated.
IPG=Interventional Procedures Guideline; LSCD=limbal stem cell deficiency
Source: CS, p61

**NHS Outcomes Framework**

The company is of the opinion that if Holoclar is recommended for use in the NHS, it would support the objectives of the NHS Outcomes Framework.[33] The introduction of Holoclar would enhance quality of life for people with long-term conditions thus improving 'Domain 2' and would support the 'overarching indicator 2' which is described as health-related quality of life (HRQoL) for people with long-term conditions.

**NHS England policies**

The company lists the NHS England policies relevant to treatment with Holoclar within the NHS and provides a commentary on the impact of the use of Holoclar on the policies (

Table 4).

Table 4 Company commentary on relevant NHS England policies

| NHS England policy | Company comments |
|---|---|
| NHS England (2014) Manual for prescribed specialised services 2013/14. Chapter 13. D12 - Adult specialist ophthalmology services.[34] | NHS England is the responsible commissioner for specialised ophthalmology services, and the Manual for Prescribed Services states that the NHS Commissioning Board (NHS England) commissions the following specialist services, including emergency care, for corneal disorders (severe anterior segment inflammation, high risk keratoplasty, endothelial keratoplasty, keratoprosthesis, collagen cross linking, excimer laser to treat corneal pathology), as well as oculoplastic surgery. NHS England has stated that the responsibility for commissioning ex vivo expanded autologous human corneal epithelial cells (Holoclar) sits with NHS England (not CCGs). |
| NHS England (2013) NHS standard contract for specialised ophthalmology (adult). Schedule 2 - the services - A. The specifications.[35] | The NHS standard contract for specialised ophthalmology services, states that current commissioned treatments by NHS England include 'Ocular surface reconstruction- keratolimbal allografts, ex vivo stem cell allografts, cultured oral mucosal epithelial transplant, conjunctival limbal autograft (living related also). |
| NHS England (2013) 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults). Particulars, schedule 2- the services, a- service specification.[36] | The NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults) is not expected to be impacted as it is not a direct comparator to ex vivo expanded autologous human corneal epithelial cells (Holoclar).<br>However, should improved success rates be seen in clinical practice compared with current treatment options, it is possible that the need for this intervention might be decreased from this patient group who may latterly be candidates for this treatment.<br>As such it is expected that a variation to the NHS specialised ophthalmology contract, or more likely the creation of a separate service specification and contract for ex vivo stem cell autografts will need to be created by NHS England to commission this service. |

CCG=clinical commissioning group
Source: CS, p62

## *2.3 Issues relating to current clinical practice*

The company makes the point (CS, p63) that all transplantation procedures (Holoclar, CLAU, KLAL) require essential pre-operative screening and post-operative follow-up procedures and that the costs of these procedures to the NHS are not reflected in the current codes for CLAU,

CLAL and KLAL. Based on clinical opinion, the company has listed the pre- and post-operative procedures associated with CLAU, CLAL and KLAL (CS, p64 to p66).

## 2.4 Innovation

The company puts forward the case that Holoclar is an innovative product (CS, p37). The company reports:

- The use of somatic stem cells taken from the intended patient offers major advantages (in comparison to embryonic stem cells) and allows for immediate therapeutic application.
- Holoclar offers several advantages over comparator technologies to transplant conjunctival-limbal or keratolimbal tissue in patients with LSCD, including lack of immunological rejection and hence the avoidance of immunosuppression, smaller amount of donor tissue required, the ability to treat both eyes and the possibility of retreatment if required. Holoclar may also offer a bridge to subsequent successful keratoplasty for some patients with LSCD complicated by deep stromal scarring, which in turn can further significantly improve VA.[13]
- Holoclar is the first ATMP containing stem cells to receive a Marketing Authorisation in Europe. To date there is no stem cell product with regulatory authority approval outside of the EU. This breakthrough in personalised, regenerative medicine responds to an unmet medical need for a rare and seriously debilitating orphan condition.
- Holoclar represents the first time that the ATMP Regulation (EC 1394/2007) has been successfully applied to a living cell-based product. However, as the development work for Holoclar was largely completed prior to the introduction of the ATMP Regulation, this required a novel regulatory approach reliant solely upon retrospective data, yet despite this, substantial numbers of patients for a rare condition (n=148) were included in the studies of Holoclar.[13] For all these reasons, the recommendation to approve Holoclar is considered one of the most significant milestones achieved by the EMA in the last 20 years.[37]
- Holoclar has been named one of four finalists shortlisted for an award in innovation and research – the UK Prix Galien Orphan Product award. A Prix Galien award is widely regarded as the highest distinction to bestow upon a pharmaceutical product.

## 2.5 Company's estimate of the number of patients eligible for treatment with Holoclar in the NHS

The company estimates that a maximum of 121 patients are likely to be currently eligible for treatment with Holoclar in the NHS in England (Table 5). The company also estimates that, in addition to the prevalent population, there are likely to be 13 new cases of severe chemical corneal injury each year (estimated incidence of 0.02 per 100,000).[14] The ERG considers that the company's estimates are reasonable.

Table 5 Company's estimates of the number of patients in England eligible for treatment with Holoclar

| Parameter | Number |
|---|---|
| Prevalence in EU of LSCD due to ocular burns[13] | 0.3 per 10,000 |
| UK population in 2014 = 64.6m[38] | 1938 |
| Number of people with LSCD in England (estimated)[38] | 1629 |
| 76% of people with LSCD are adults[38] | 1238 |
| 65% of adults with LSCD due to physical or chemical burns[39] | 805 |
| 20% of adults with LSCD due to physical or chemical burns with moderate to severe LSCD[39] | 161 |
| 75% of adults with LSCD due to physical or chemical burns with moderate to severe LSCD likely to receive surgical treatment[39] | 121 |

EU=European Union; LSCD=limbal stem cell deficiency; UK=United Kingdom.
Source: CS, p60 and p61

# 3 CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

.

Table 6 summarises the decision problem described by the company in the CS[1] in relation to the final scope issued by NICE.[40] Each parameter is discussed in more detail in the text following the table.

Table 6 Final scope issued by NICE, company and ERG comments

| **NICE scope**<br>**Parameter and specification** | **Decision problem addressed in the company submission** | **ERG comment** |
|---|---|---|
| Population<br>Adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2mm$^2$ of undamaged limbus | As per final scope | Agree. However, the ERG notes that there is no clinical effectiveness evidence presented in the CS for the use of Holoclar in patients with bilateral LSCD |
| Intervention<br>Ex vivo expanded autologous human corneal epithelial cells containing stem cells | As per final scope | Agree |
| Comparator(s)<br>For people with unilateral LSCD<br>• conjunctival limbal autograft<br>• BSC<br>For people with bilateral LSCD<br>• conjunctival limbal autograft<br>• limbal epithelial stem cells allografts<br>• BSC | As per final scope | The ERG agrees with the company that limbal epithelial stem cells allograft is a relevant comparator for unilateral LSCD<br><br>The company presents evidence for conjunctival limbal autograft for people with bilateral LSCD but the ERG agrees with the company that this is not an appropriate comparator for this patient group |
| Outcomes<br>• clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation<br>• symptoms of LSCD including pain, burning and photophobia<br>• VA (the affected eye)<br>• VA (the whole person)<br>• AEs<br>• HRQoL | As per final scope | The ERG notes that there are no HRQoL data presented in the clinical effectiveness section of the CS |
| Economic analysis<br>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye | As per final scope | Agree. However, the company does not explicitly present scenarios describing the treatment of best and worst seeing eyes |

| NICE scope<br>Parameter and specification | Decision problem addressed in the company submission | ERG comment |
|---|---|---|
| Other considerations<br>The costs and effects of BSC when given in combination with the intervention should be taken into account. Best supportive care includes topical steroids, ocular lubricants, bandage contact lenses, autologous serum eye drops, oral and/or topical vitamin C and oral tetracycline | **Issues related to equity or equality**<br>For Armed Forces personnel who acquire moderate to severe LSCD due to physical or chemical ocular burns sustained during service, e.g. due to explosive devices, the impact of LSCD in this group (unilaterally or bilaterally) may be further complicated by concomitant loss of limb and other life-threatening or life-changing injuries. As such, this group is disproportionately affected by physical disabilities, and other mental health sequelae, which differ to the general population of patients with moderate to severe LSCD due to physical or chemical ocular burns. A significant equality issue may therefore be created if Holoclar is not recommended for use within the NHS in England, contrary to the Armed Forces Covenant | The ERG does not consider this to be an equality or equity issue |

AE=adverse events; BSC=best supportive care; CS=company submission; ERG=Evidence Review Group; HRQoL=health related quality of life; LSCD=limbal stem cell deficiency; QALY=quality adjusted life year
Source: NICE Final scope and CS, Table 1

## *3.1 Holoclar clinical evidence*

The ERG is aware that the treatment of LSCD due to ocular burns is a highly specialised area and notes that LSCD due to burns to the eyes is considered a rare condition by the EMA.[13] The number of patients treated each year is small and there is a limited number of treating clinics and clinicians in the UK NHS. There is no standard NHS treatment pathway and patient care may differ according to treatment centre.

There is no direct clinical evidence comparing Holoclar with any of the comparators listed in the final scope issued by NICE. The company provides clinical effectiveness evidence to support the clinical effectiveness of Holoclar from three unpublished case series studies HLSTM01,[41] HLSTM02[42] and HLSTM04.[43] In the CS, the company has focussed on the HLSTM01[41] study, a retrospective case series study of 104 patients with moderate to severe LSCD due to ocular burns who were treated with Holoclar in two Italian ophthalmology centres between 1998 and 2008. The stated duration of study follow-up is 12 months; however, there is a small group of patients for whom later data are available. The company also presents the results of five published, non-randomised, non-comparative studies[44-48] that describe the use of Holoclar in patients with moderate to severe LSCD; however, the majority of the data from the published studies is encompassed in the HLSTM01 case series study. The ERG notes that the evidence presented in the CS to support the clinical effectiveness of Holoclar is for the treatment of unilateral LSCD.

The company stated that it was inappropriate to carry out any direct or indirect clinical effectiveness treatment comparisons between Holoclar and any of the comparators listed in the final scope issued by NICE due to a lack of comparable clinical data. The company's systematic review did not identify any relevant randomised controlled trials (RCTs) that included the intervention specified in the final scope issued by NICE (see Table 1 for more details on comparators). The company's systematic review of evidence for the comparators

specified the final scope issued by NICE identified one randomised study[49] of 20 patients with unilateral LSCD who were treated with either CLAL or KLAL. However, the majority of available studies investigating the treatment of moderate to severe LSCD are largely observational and non-comparative. The company points out (CS, p112) that data from the studies are heterogeneous with differences in patient populations, culture methods, carrier substrates, length of follow-up and evaluation methods (see Section 3.4 of this ERG report for further discussion of the comparator studies).

The company also points out (CS, p112) that the majority of the clinical effectiveness evidence presented is only relevant to patients with unilateral moderate to severe LSCD.

The company has provided a narrative summary of the relevant comparator studies in the CS (CS, Table 12 and Table 14). The ERG agrees that given the data available, clinical effectiveness comparisons between Holoclar and the treatments specified in the final scope issued by NICE are not feasible. However, the company has carried out cost effectiveness comparisons.

## *3.2 Population*

The population described in the CS matches the population described in the final scope issued by NICE (i.e. adults with moderate to severe LSCD [defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA] unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus). This is the same population as described in the conditional licence for Holoclar issued by the EMA.[30]

*Treatment of unilateral and bilateral LSCD*

The company states that one of the major benefits of Holoclar is that it can be used bilaterally in patients that have at least 1-2$mm^2$ of healthy limbus in one eye. The company goes on to construct two separate economic models for the treatment of one eye (unilateral LSCD) and two eyes (bilateral LSCD). When used bilaterally, Holoclar is undertaken in both eyes at different times, 12 months apart. The company's labelling of the models is confusing. The company uses the term 'unilateral LSCD' to refer to the model that includes patients who have only one eye treated. However, the ERG recognises that, in the real world, there are patients with bilateral disease who would only ever have one eye treated. The company uses the term 'bilateral LSCD' to refer to the model that includes patients who have two eyes treated. Again, the ERG recognises that, in the real world, not all patients with bilateral LSCD will have both eyes treated.

During the clarification process, the ERG requested access to patient-level data from the HLSTM01 case series study asking the company to indicate whether patients had unilateral or bilateral LSCD. The company replied that, as this information was not recorded on the HLSTM01 Case Report Form, it was not possible to distinguish between unilateral and bilateral groups. However, the company was able to confirm that one patient had received Holoclar treatment in both eyes.

To use the clinical effectiveness data submitted by the company to support decision-making, it is necessary to make an assumption about the proportion of people within the HLSTM01 dataset who had unilateral and bilateral disease and then appraise the usefulness of the dataset to provide evidence for each of the indications individually. Advice from clinical experts and text in the CS suggest that in clinical practice the proportion of people with bilateral disease is about 10%.

The ERG considers that, although imperfect, it is acceptable to use the whole of the HLSTM01 case series study data to provide clinical effectiveness evidence for the unilateral use of Holoclar in patients with moderate to severe LSCD even though the population will likely consist of some patients with bilateral disease only having one eye treated. The use of the same dataset to support the bilateral use of Holoclar, however, is more much difficult to justify. Outcomes for bilateral patients receiving Holoclar in one or both eyes are impossible to determine from the HLSTM01 dataset provided by the company; for example, a single case study is not sufficient evidence to provide support for using Holoclar in both eyes for patients with moderate to severe LCSD.

In the absence of any clinical evidence to support using Holoclar bilaterally, the company has made the assumption that bilateral transplantation has the same success rate as unilateral transplantation. The ERG considers that this is unlikely to be the case for several reasons:

- Holoclar requires a biopsy of 1-2mm$^2$ of undamaged limbus for biopsy. In the bilateral case this has to be taken from a damaged eye. The company assumes that there is no difference in patient outcomes whether the limbal cells are taken from a damaged or undamaged eye. If this is true, it is unclear to the ERG why, during a unilateral intervention, the biopsy is performed on the healthy eye and not on the eye that is already damaged (but has some healthy limbus). This approach suggests to the ERG that there must be a clinical reason underlying the decision to take a biopsy from the healthy eye rather than from the damaged eye; whether this rationale is related to improved efficacy and patient outcomes is not known. The ERG speculates that it may be more difficult to locate and extract healthy limbal cells from a damaged eye than from a healthy eye.

- The company has assumed that the same number of biopsies can be taken from a healthy eye as from a damaged eye. Whether using a damaged or undamaged eye, the company states that there is a 10% chance that the first biopsy will fail. The company goes on to state that the Holoclar transplant itself can be carried out up to three times even if the first and second transplants fail. This means that a total of six biopsies could be required from a damaged eye that may only have 1-2mm$^2$ of undamaged limbus. The ERG does not consider this to be plausible. By default, that means that, even if the success rate per transplant is the same, overall efficacy of bilateral transplantation will be lower than the efficacy of unilateral transplantation simply due to the lower number of transplants that could be performed in patients undergoing bilateral intervention.

The company also states that multiple grafts can be grown from a single biopsy and that these can be frozen and used should the initial graft fail. This would potentially allow for only a single biopsy to be taken from a damaged eye and be used bilaterally if required. However, the company presents no evidence on the success rates with frozen and defrosted grafts nor does it indicate what the costs of this option would be. As such, the ERG considers that this approach should not be considered in the CS and the company rightly does not include it as an option in the economic model.

Given the clinical reasons to doubt the equal efficacy of using Holoclar unilaterally and bilaterally, and the absence of supportive clinical effectiveness evidence available, the ERG considers the assumption of equal efficacy to be unfounded.

## *3.3 Intervention*

Holoclar has been licensed in Europe since February 2015 for the treatment of adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2mm$^2$ of undamaged limbus is required for biopsy. The marketing authorisation is conditional on the company providing the results from an on-going prospective, European, uncontrolled phase IV study known as HLSTM03[50] (or HOLOCORE). The company expects the results of the study[50] to be available in 2020.

A regimen of post-implantation treatment is stipulated in the EMA marketing authorisation[13] for Holoclar. The regimen includes antibiotics (doxycycline or amoxicillin), prednisone, topical corticosteroids and dexamethasone eye-drops. Specific details are provided in the CS (p36) and in the SmPC.[30]

## *3.4 Comparators*

In the final scope issued by NICE, the comparators for people with **unilateral** LSCD are listed as conjunctival limbal autograft and BSC only.

The ERG notes that in the final scope issued by NICE, limbal epithelial stem cells allograft is not listed a comparator for patients with unilateral LSCD. Clinical advice to the ERG is that limbal epithelial stem cells allografts (e.g., Lr-CLAL and KLAL) are used in the UK to treat unilateral LSCD.

The comparators for people with **bilateral** LSCD are conjunctival limbal autograft, limbal epithelial stem cell allografts and BSC.

After consultation with clinical experts, the company is of the opinion (CS, p112) that in the UK NHS, conjunctival limbal autograft (e.g., CLAU) is not used to treat patients with bilateral LSCD.[21,51] Clinical advice to the ERG is that patients with bilateral LSCD are unlikely to be treated with CLAU.

The company puts forward a number of caveats (CS, p20 and p112) when reviewing the evidence for the clinical effectiveness of the **comparators**:

- The available studies investigating the treatment of moderate to severe LSCD are largely observational and non-comparative
- Data from the studies are heterogeneous with differences in patient populations, culture methods, carrier substrates, length of follow-up and evaluation methods
- Data reported in the studies were collected over a period of 30 years; transplant methodology and BSC practice have evolved during that time
- The literature is likely to be open to several types of bias, including selection bias, assessment bias and publication bias.

The ERG agrees with the company that the available evidence describing the clinical effectiveness of the comparators should be viewed with considerable caution.

***3.5 The ERG is aware of emerging techniques that are currently being trialled in different treatment centres and in different countries to treat moderate to severe LSCD due to ocular burns. Examples of the emerging techniques include the Simple Limbal Epithelial Transplantation (SLET) procedure[52] and an ex-vivo expanded limbal stem cell transplantation method that is being trialled at the University of Newcastle.[53] Clinical advice to the ERG is that the SLET procedure can be used to treat patients in the NHS and, given the relative simplicity of the procedure, the use of SLET in the NHS is likely to increase. Publications relevant to SLET[52] and the work conducted at Newcastle[53] were excluded from the company's systematic review of comparator technologies on the grounds that they are outside of the scope because they do not address the efficacy, safety or impact on HRQoL of CLAU, CLAL or KLAL (CS, Appendix 4, p30 to p34). The ERG considers that SLET[52] and Newcastle's ex vivo expanded limbal stem cell transplantation system[53] are examples of non-standard CLAU and considers that both treatments are outside of the present scope as they are not routinely used in the UK NHS.***

***Outcomes***

Clinical evidence for the efficacy of Holoclar is reported in the CS for the majority of the outcomes specified in the final scope issued by NICE, i.e., clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation, symptoms of LSCD including pain, burning and photophobia, VA and adverse effects (AEs) of treatment. The outcomes from the HLSTM01[41] case study are reported post-operatively at 12 months. Health-related quality of life data (HRQoL) data pertaining to Holoclar are not presented in the clinical effectiveness section of the CS.

## *3.6 Economic analysis*

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 50-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective. Costs and benefits were discounted at 1.5% per annum. The ERG is aware that the NICE Guide to the Methods of Technology Appraisal[54] states that an annual discount rate of 1.5% may be considered if the treatment restores people with severely impaired quality of life to full health for their remaining lifetime. However, the ERG considers that treatment with Holoclar does not meet this criterion (see Section 5.5.3 of this report) and that costs and benefits should therefore be discounted at the current NICE Reference Case value of 3.5% per annum.[54]

## *3.7 Subgroups*

According to the economic analysis section of the final scope issued by NICE, the cost effectiveness analysis should include consideration of the benefit in the best seeing and worst

seeing eyes. In the company's unilateral LSCD model, by definition, the worst seeing eye is treated. In the company's bilateral LSCD model, by definition, both eyes are treated. This means that the company has not directly considered the subgroups listed in the final scope.

## *3.8 Other considerations*

### 3.8.1 Equity considerations

In Table 1 and on pages 66 and 67 of the CS, the company discusses the Armed Forces Covenant which states that members of the armed forces community 'should face no disadvantage compared with other citizens in the provision of public and commercial services; and that special consideration is appropriate in some cases, especially for those who have given the most such as the injured or bereaved.'

The company highlights that people who have LSCD due to chemical or ocular burns incurred whilst serving in the armed forces are likely to also have experienced the loss of limbs or other life changing events or injuries, both physical and mental. The company argues that people from the armed forces with moderate to severe LSCD due to ocular burns are disproportionately affected by physical disability and resulting mental health problems compared to the general population of people with moderate to severe LSCD due to ocular burns. The company further argues that the restoration of eyesight has a greater impact on people with other disabilities than might be captured in the QALY calculation.

It is the company's opinion (CS, p67) that if Holoclar is not made available to the NHS in England, a significant equality issue would arise for patients with LSCD due ocular burns that were incurred whilst serving in the armed forces. The company highlights that these patients are likely to also have experienced the loss of limbs or other life changing events or injuries, both physical and mental, over and above those experienced by the general population of patients with the same condition. The ERG does not consider this to be an equality or equity issue.

# 4 CLINICAL EFFECTIVENESS

This section provides a structured summary and critique of the clinical effectiveness evidence submitted by the company in support of the use of Holoclar for the treatment of patients with moderate to severe LSCD due to ocular burns.

### 4.1.1 Systematic review methods

The company conducted a systematic review to identify studies of relevance to the appraisal under discussion. A summary of the systematic review methods employed by the company, with accompanying ERG comments, is presented in Table 7. Full details of the systematic review are provided in the CS (Section 4.1 and in Appendix 4). The company carried out a systematic review to identify evidence for the clinical effectiveness of Holoclar and a separate systematic review to identify evidence for the effectiveness of the comparator treatments.

Overall, the ERG is satisfied that the company's systematic review methods were of a good standard, and the objectives were relevant to the final scope issued by NICE and to the decision problem.

Table 7 Summary and ERG comment on the systematic review methods used by the company

| Review method | ERG comment |
|---|---|
| **Searching** | |
| • RCT and non-RCT data searches<br>• Databases searched included Medline, Medline in Process, Embase and CENTRAL (search strategies are described in Appendix 4 of the CS) from January 1989 to 4th January 2016<br>• Grey literature was searched for clinical studies and conference abstracts | • The ERG was able to replicate the searches<br>• The company searched the appropriate conference abstracts<br>• The ERG is confident that no relevant studies were missed |
| **Eligibility criteria** | |
| • Two independent assessors assessed study eligibility | • Use of two independent assessors improves the quality of reviews<br>• English and non-English language publications were considered by the company<br>• The ERG agrees with the company's rationale to simplify the inclusion criteria and limit to patients with a confirmed diagnosis of LSCD |
| **Data extraction** | |
| • Two independent assessors extracted data<br>• A pre-defined extraction form was used | • The company has not reported the method used to extract study data Quality assurance regarding data extraction is therefore uncertain<br>• The company contacted study authors for missing information |
| **Quality assessment and risk of bias** | |
| • Descriptive critical appraisal of all studies was undertaken using the NICE recommended method[55] | • Unclear if two independent assessors were employed<br>• No RCT evidence was presented in the CS for treatment with Holoclar. The Joanna Briggs appraisal tool for case series[56] was applied to the studies of Holoclar and to all the identified comparator studies. The ERG considers this approach to be appropriate except that one of the comparator studies was a randomised trial and should have been assessed with an appropriate tool |

LSCD=limbal stem cell deficiency; RCT=randomised controlled trial; CS=company submission
Source: CS, p68 to p71

### 4.1.2 Evidence synthesis

The company did not identify any relevant RCTs comparing Holoclar with any treatment in patients with moderate to severe LSCD due to ocular burns. The company identified five published[44-48] and three unpublished[41-43] non-RCTs (CS, p75).

The main focus of the CS is an unpublished case series study known as HLSTM01[41] with supporting evidence from two other related unpublished studies, HLSTM02[42] and HLSTM04.[43]

The company provides a narrative summary of all of the studies describing the clinical effectiveness of the comparators that are listed in the final scope issued by NICE (Table 12 and Table 14 of the CS).

The company's systematic review of comparator technologies identified 25 relevant studies. The company reports that 22 of the studies yield data pertinent to the outcomes measures specified in the final scope issued by NICE. The results of the systematic review of comparator technologies are discussed in section 4.7 of this ERG report.

The company was unable to carry out any direct or indirect comparisons between Holoclar and any of the comparators listed in the NICE scope due to a lack of comparable data across the identified studies.

## *4.2 Critique, analysis and interpretation of trials of the technology*

In response to the ERG's clarification request, the company explained the relationship between the five published studies[44-48] and the unpublished studies[41-43] of Holoclar presented in the CS (Table 8).

Details of the five published studies[44-48] are provided in Table 10 and Table 12 of the CS. A narrative summary of the results of the five published studies[44-48] is presented in Section 4.11.5 of the CS.

Table 8 Relationship between the five published studies of Holoclar and the three HLSTM case series studies

| Study ID | Number of patients | Relationship with HLSTM01/2/4 case series studies |
|---|---|---|
| Pellegrini 1997[46] | 2 | There is no overlap between the patient population reported in this pilot study and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies |
| Rama 2001[47] | 18 | 6 of the 18 patients whose results are included in this publication were also included in the HLSTM01 study. There is no overlap between the patient population reported in Rama 2001 and the patient populations reported in the HLSTM02 and HLSTM04 studies |
| Rama 2010[48] | 112 | 93 of the 112 patients whose results are included in this publication were also included in the HLSTM01 study. There is no overlap between the patient population reported in Rama 2010 and the patient populations reported in the HLSTM02 and HLSTM04 studies |
| Marchini 2012[44] | 16 | There is no overlap between the patient population reported in this study and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies |
| Pellegrini 2013[45] | 152 | There is almost complete overlap between the patient population reported in this study and the patient populations reported in the HLSTM01 and HLSTM02 studies. Out of the 152 patients included in the publication, 133 are included in the studies HLSTM01 and HLSTM02 studies. There is no overlap between the patient population reported in Pellegrini 2013 and the patient population reported in the HLSTM04 study |

ID= identification
Source: Company clarification response to QA2

### 4.2.1 Key studies presented in the company submission

The characteristics of the three unpublished case series studies of Holoclar (HLSTM01,[41] HLSTM02[42] and HLSTM04[43]) are described in Table 9. The main difference between the HLSTM01 case series study and the HLSTM02 case series study is related to treatment centre. The patients included in the HLSTM01 case series study were treated at two centres (in Milan and Rome); both centres used the same standard treatment protocol.

The patients included in the HLSTM02 case series study were treated at seven other centres in Italy.

The data included in the HLSTM04 case series study are derived from all patients who were treated with Holoclar from 2008 onwards (after the end of the period of data collection for HLSTM01 and HLSTM02). The 15 patients included in the HLSTM04 case series study were treated at three centres in Italy.

The company states (CS, p122) that 219 patients in total had been treated with Holoclar between 1998 and 2007 (HLSTM01 and HLSTM02). Of the 219 treated patients, data from 135 were available for inclusion in the HLSTM01 and the HLSTM02 case series studies. The company reports that data for the remaining 82 patients were not made available to the company by the investigators in the treatment centres. The ERG notes that 82 missing patients added to 135 included patients means that a total of 217 patients were treated (not 219). The company discusses the implications of the missing data in the CS but does not explain why the focus is on 219, rather than 217 patients (CS, p122 and p123). The ERG notes from the CS (CS, p126) that 106 patients were originally recruited to the HLSTM01 case series study; however only 104 patients were included in the ITT analysis. The ITT population was defined as patients who were treated with Holoclar and had a follow-up visit at least 6 months after the surgery.

Table 9 Characteristics of the HLSTM01, HLSTM02 and HLSTM04 case series studies

| Study | Study location and design | Intervention | Study population | Primary Outcomes | Secondary Outcomes | Duration of follow-up | Missing data |
|---|---|---|---|---|---|---|---|
| HLSTM01<br>Italy | Retrospective, uncontrolled, multicentre case-series non-randomised, | Ex vivo cultured ACLSCT Holoclar<br><br>(n=104) | Moderate to severe unilateral or bilateral LSCD due to ocular burns. A total of 106 patients who underwent at least one ACLSC transplantation were included in the study | Success based on: superficial corneal NV as 'none' or 'mild'; epithelial defects classified as 'none' (no staining) or 'tracing' (minimum staining) | Change in symptoms (pain, burning, photophobia), inflammation and VA. Number of ACLSCTs in each patient. Number of successful keratoplasties after ACLSCT. Evaluation of impression cytology: percentage of K3+, K3-, K12+, K12-, K19+, and K19- cells, and presence of caliciform cells | 12 Months | A sensitivity analysis was performed using the following two methods:<br>1) NOCB: Missing data at the endpoint visit were replaced by data available at the next closest visit;<br>2) Zero imputation: Missing data at the endpoint visit were considered a Failure (i.e. with neovascularisation). |
| HLSTM02<br>Italy | Retrospective, uncontrolled, multicentre case-series | Ex vivo cultured ACLSCT Holoclar<br>(n=29) | Moderate to severe unilateral or bilateral LSCD due to ocular burns. A total of 31 cases attended the pre-surgical visit: 29 underwent limbal biopsy and surgery for transplantation, and were included in the study | Number of subjects experiencing AEs and the number of AEs | Rate of ASCLCT recorded as success or failure based on investigator's judgement. Number of ASLSCTs in each patient. Number of successful keratoplasties after transplantation | ≥1 year | Secondary efficacy data were analysed as observed, without replacement for missing values. |
| HLSTM04<br>Italy | Retrospective, uncontrolled, multicentre case-series | Ex vivo cultured ACLSCT Holoclar<br>(n=15) | Moderate to severe unilateral or bilateral LSCD due to ocular burns. All patients started the treatment procedure (i.e. underwent biopsy) from 2008 to present | Safety and efficacy of ACLSCT in restoring normal and corneal epithelium | Safety of ACLSCT, including biopsy, surgical procedure and post-surgical treatments in terms of AEs, SAEs, ADRs and serious ADRs | ≥3 months | No imputation technique was applied to estimate missing values. |

ACLSC = autologous cultured limbal stem cell; ACLSCT=autologous cultured limbal stem cell transplantation; ADR=adverse drug reaction; AE=adverse event; LSCD=limbal stem cell deficiency; NOCB=next observation carried backward; NV=neovascularisation; SAE=serious adverse event; VA=visual acuity
Source: Clinical study report and CS, adapted from Table 11

This section of the ERG report focuses on the HLSTM01 case series study only. Details and outcomes of the HLSTM02 and HLSTM04 case series studies are included in Appendix 2 of this ERG report.

**Case series study design**

The main evidence presented in the CS is derived from non-randomised, non-controlled and retrospective case series studies. A case series study is a type of descriptive observational study where the main purpose is to follow a group of patients who have the same diagnosis or who are undergoing the same procedure over a certain period of time. Case series studies are not designed to test the hypothesis of treatment efficacy.[57]

Advantages of case series studies include high external validity if they enrol a wide range of patients with different characteristics and co-interventions and they are relatively inexpensive to run.

The disadvantages of case series studies are many. First, lack of randomisation and lack of comparison group mean that conclusions cannot be made about the effect of treatment on outcomes, as outcomes may be linked to treatment or to other patient characteristics. Lack of randomisation is a critical limitation as the investigators may favour their treatment of choice. Case series studies are susceptible to selection bias and measurement bias. Selection bias is present in case series studies when follow-up data are less likely to be collected from patients who are either performing better or worse than others, or if patients are not consecutively enrolled. Measurement bias is present in case series studies when different methods are used to measure the same outcome in different patients.

Kooistra[58] has proposed criteria for evaluating the design, analysis and reporting of case series studies and the ERG has applied the criteria to the HLSTM01 case series study. A description of the criteria can be found in Appendix 1.

The study question being addressed in the HLSTM01 case study is focussed and clearly set out. The inclusion and exclusion criteria are well defined and the intervention is described in detail. There is no information to indicate whether patients were included in the study consecutively; this means it is difficult to ascertain whether the inclusion period was short. The study also only explores efficacy and safety based outcomes; outcomes measuring patient satisfaction or mental wellbeing have not been included. A masked independent assessor assessed the primary efficacy outcome (i.e., treatment success or failure). However, one of the secondary outcomes, symptom resolution, was not assessed in this way. The baseline patient characteristics are described, but no explanation is provided for reasons why patients were lost to follow-up. The study authors explain the presence, direction and magnitude of

bias in detail (CS, Section 4.11.4). The authors do not draw absolute conclusions from their data; however, they make statements about the statistical significance of the outcomes and report p-values. Overall, the ERG considers that the HLSTM01 case series study is flawed as hypothesis testing has been carried out, there is lack of information about patient drop out and there are missing data.

## *4.3 Quality assessment of the HLSTM01 case series study*

The company appraised the HLSTM01 case series study using the Joanna Briggs Institute (JBI)[56] checklist for case series studies. The JBI checklist includes 10 items, each of which is scored as *yes*, *no*, *unclear* or *not applicable*. The company states (CS, p118) that in its assessment, a *yes* response was marked as 1, whilst all the other possible responses were marked as zero. In this way, a maximum of 10 points could be awarded per study. The company reports that the HLSTM01 study scored nine, suggesting a low risk of bias.

The ERG does not completely agree with the company's assessment (Table 10). The ERG did not have sufficient information to allow an assessment of one of the JBI criteria (whether the case series had consecutive inclusion of participants). The ERG considers that the company has not provided sufficient data on long-term follow-up and has carried out hypothesis testing. Hypothesis testing suggests that Holoclar is effective in spite of the aim of case series being to describe the data and not to form any conclusions. Therefore, the ERG is of the opinion that the case series study may have a greater risk of bias than the company claims.

Table 10 Company's assessment of the risk of bias for the HLSTM01 case series study with ERG comment

| JBI checklist criteria | Company assessment | ERG comment |
|---|---|---|
| Were there clear criteria for inclusion in the case series? | 1 | Agree |
| Was the condition measured in a standard, reliable way for all participants included in the case series? | 1 | Agree |
| Were valid methods used for identification of the condition for all participants included in the case series? | 1 | Agree |
| Did the case series have consecutive inclusion of participants? | 1 | The ERG is unclear how the company has assessed this criterion as sufficient information is not provided in the protocol or CSR to assess whether the case series studies have consecutively included participants or not |
| Did the case series have complete inclusion of participants? | 0 | Agree |
| Was there clear reporting of the demographics of the participants in the study? | 1 | Agree |
| Was there clear reporting of clinical information of the participants? | 1 | Agree |
| Were the outcomes or follow-up results of cases clearly reported? | 1 | The ERG agrees that outcomes of case series studies have been clearly reported, however sufficient long-term follow-up data have not been provided for the patients in the case series studies |
| Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 1 | Agree |
| Was statistical analysis appropriate? | 1 | The ERG disagrees that the statistical analysis was appropriate for HLSTM01 as hypothesis testing has been carried out |
| Score | 9 | |

CSR=clinical study report; ERG=evidence review group
Source: CS, Appendix 4

## *4.4 Study characteristics*

The study characteristics of the HLSTM01 case series studies are shown in Table 9. The ERG is aware that the number of patients included in the HLSTM01 study (n=104) is substantial, given the rarity of the condition. As noted in Section 4.2.1 of this ERG report, the HLSTM01 case series study was conducted in 106 patients. The 104 patients in the ITT population were those who had received treatment with Holoclar and had a control visit at least 6 months after transplantation.

The ERG notes that the duration of follow-up for the HLSTM01 and the HLSTM02 case series studies is 1 year.

## 4.5 Patient characteristics

The demographic characteristics of the patients in the HLSTM01 case series study are presented in Table 11. Clinical advice to the ERG is that the patients in the studies are representative of patients with moderate to severe LSCD who would be treated in the NHS.

Table 11 Patient baseline characteristics in the HLSTM01 case series study

| | **HLSTM01 N=104** |
|---|---|
| Mean age (standard deviation) | 46.8 (14.4) |
| Age range | 13.7 to 79.1 |
| Male n (%) | 80 (76.9) |
| Time from injury to treatment with Holoclar | 18.4 years |

Source: CSR for HLSTM01

## 4.6 Results from the HLSTM01 study

The results of the HLSTM01 case series studies discussed in this section are only for the outcomes specified in the final scope issued by NICE. All other study results are available in Section 4.11.5 of the CS. The ERG notes that all outcomes are reported after 1 year of follow-up. The company reports that HRQoL data were not collected.

The ERG notes that, for the HLSTM01 case series study, the company has presented p-values and conducted formal testing. However, this study is a case series study and the ERG considers that the results of any formal testing are invalid. For this reason, the ERG has not reported any p-values in this section.

The primary aim of the study was to determine the clinical efficacy of Holoclar. The ITT population included 104 patients with the per-protocol population including 99 patients.

The primary efficacy endpoint was rate of success of Holoclar transplantation based on stable corneal epithelium without significant recurrence of neo-vascularisation at 12 months post-intervention. In the ITT population (including missing data imputed as failure), success was reported in 75 patients (72.1%; 95% CI: 62.5 to 80.5%). Results of the sensitivity analysis excluding missing data were similar (75.8%; 95% CI: 66.1 to 83.8%). A masked independent assessor evaluated the results where data were available at both baseline and 12 months (n=46); the evaluation results suggested that the treatment was a success in 31 out of 46 cases (67.4%).

A secondary endpoint of the study is VA measured as both natural and best refracted using the Snellen chart and values expressed according to tenth scale. The results for VA suggest an improvement by at least one line in 49% of patients (95% CI: 39.4% to 58.6%) and in 83.3% (95% CI: 66.1 to 100%) of patients without stromal scarring (15/18).

The numbers of patients with symptoms at pre-surgical assessment and at 12 months post-surgery are displayed in Table 12. The results highlight that the number of patients with symptoms significantly decreased during the time between the pre-surgical assessment and 12 month post-surgery.

Table 12 Numbers of patients with symptoms at pre-surgical assessment and 12 months post-surgery

| Symptoms of LSCD | HLSTM01 (N=104) Pre-surgical assessment n (%) | HLSTM01 (N=104) 12 months post-surgery n (%) |
|---|---|---|
| Any symptoms | 40 (38.5) | 12 (11.5%) |
| Pain | 7 (6.7) | 0 (0)*^ |
| Burning | 30 (28.8) | 7 (6.7) |
| Photophobia | 35 (33.7) | 8 (7.7) |

LSCD=limbal stem cell deficiency;
Source: CS, p127
*based on 97 patients
^The value was corrected after the second committee meeting.

**Adverse events**

The company reports (CS, p160) the following AEs:

- Six serious adverse events (SAEs) (three were fatal) after six transplantation procedures (5.3%) all in patients who had had one transplant. None of the SAEs was considered to be treatment-related.
- There were 22 adverse drug reactions (16.8%) after 19 transplantations.
- There was one case of gastritis and five cases of glaucoma that were possibly related to treatment with corticosteroids. One case of glaucoma was considered to be treatment-related.

## *4.7 Company mitigation of potential bias in the three unpublished case series studies*

Exploration of study biases is very important, especially in studies of patients with rare diseases where there is limited published evidence. The company outlined the procedures that were undertaken in order to mitigate against potential bias in the unpublished Holoclar studies.

The company reports (CS, p122) that a protocol and statistical analysis plan (SAP) were generated prospectively. The protocol and SAP detailed how to collect and evaluate the retrospective data. The ERG considers that the protocol and SAP are of a good standard and confirms that all of outcomes and analyses were pre-specified.

The company re-evaluated some study outcomes using independent masked assessment. However, as only some of the efficacy outcomes (for some patients) were independently assessed, this raises concern over whether the other efficacy outcomes were influenced by the investigators in any way.

The company also addresses bias relating to the level of missing data present in the Holoclar studies. From the 219 patients included in the Holoclar studies, data are only available for 135 (61.6%) patients. The company explains that data for the remaining 82 patients were not available as the investigators declined an invitation to participate and provide the clinical data. As noted in Section 4.2.1 of this ERG report, the ERG is uncertain of the exact number of missing cases as the company's calculation (135 + 82) results in a total of 217 patients treated with Holoclar and not 219.

The company was unable to provide the reasons for the investigators' non-participation. The company states (clarification response A8) that 'declinations were proffered in written or verbal form or alternatively, no response to repeated invitations was also considered to be a declination. The reason for an investigator declining the invitation to participate in the HLSTM01 study was not requested nor required to be stated, only that the invitation had been declined.'

The company investigated whether the missing data could have an effect on the available evidence and invalidate it in any way. The company reports two of the published studies (Marchini[44] and Rama[47]) included 25 of the 82 missing patients. The company concludes that the results of the two published studies[44,47] are comparable to the results of the HLSTM01 and HLSTM02 case series studies; the ERG is concerned that the company's attempt to investigate the potential impact of missing data is insufficiently robust to support this conclusion. The ERG considers there is a risk that the presented results from 61.6% of the 219 patients treated with Holoclar (and included in the HLSTM01 and HLSTM02 case series studies) could be biased. Further assessment is needed to allow the effects of the missing data to be evaluated.

## *4.8 Company's systematic review of comparator studies*

The company reports (CS, p75) that 25 studies[11,23,26,27,49,59-81] were identified for inclusion in the systematic review of comparator interventions and that 22 of the studies[11,23,26,27,49,59,61-63,65-74,76-81] provided outcomes relevant to the final scope issued by NICE.

In the CS, the key tables relevant to the discussion of comparator studies are Table 12 (Published studies of comparator technologies identified by the systematic literature search) and Table 14 (Outcome measures for comparator technologies).

The ERG notes that in the 'conservative surgical options' category of Table 14 there appears to be a formatting error that has resulted in the omission of one, or possibly two studies.[59,71] The studies[59,71] both report outcomes for the use of AMT in a combined total of 20 patients. The ERG notes from Appendix 4 that the Anderson[59] and Kheirkhah[71] studies were listed in an earlier version of Table 14.

## *4.9 Assessment of risk of bias of the comparator studies*

The company has conducted a quality assessment of the studies included in Table 14 of the CS in which CLAU, CLAL, Lr-CLAL or KLAL were the interventions; the company did not quality assess the studies that described BSC treatments. The studies were appraised using the JBI[56] checklist for case series studies.

The company reports (CS, p118) that: i) seven of the 22 studies warranted a score of five or greater and ii) at least 12 of the 22 studies were awarded a score of 1 on the question of the outcomes or follow-up results being clearly reported. The ERG agrees with the company's assessment, but notes that two of the studies[74,79] were reported as abstracts only; abstracts do not always provide enough information to allow for a full assessment of a study. The ERG also notes that the study by Titiyal[49] is a randomised study and therefore should have been assessed using an appraisal tool appropriate for the critique of RCTs.

## *4.10 Characteristics of the comparator studies*

### 4.10.1 Conservative management (BSC)

The company did not identify any comparative studies of the use of BSC for the treatment of moderate to severe LSCD due to ocular burns (Table 13). The company identified one case report[76] that documented the use of therapeutic scleral lenses in LSCD not due to physical or chemical burns and one prospective case series study that described conjunctival epithelial scraping in four patients with chemically induced LSCD after keratoplasty.[61] The company also identified two case series studies of the use of AMT.[59,71]

### 4.10.2 Surgical interventions

The company states (CS, p117) that the evidence for the clinical effectiveness of CLAU, CLAL and KLAL is, for the most part, derived from non-randomised, non-controlled and retrospective case series studies. The company reports that one open label, randomised study[49] was identified. In this study, 20 patients with unilateral LSCD due to ocular burns were randomised to treatment with either CLAL or KLAL.

Table 13 Key characteristics of identified comparator studies

| Study ID and location | Intervention | Study design (as described in the CS) | Number of pts (total) | Follow-up | % pts with ocular burns | % pts unilateral | % pts bilateral | % pts achieving ocular stability | % pts with improvement in VA |
|---|---|---|---|---|---|---|---|---|---|
| **BSC** | | | | | | | | | |
| Schornack 2011[76] USA | Therapeutic scleral lens | Single case (USA) | 1 | 18 months | 0% | NR | NR | Integrity of ocular surface maintained | NR |
| Dua 1998[61] UK | Conjunctival epithelial scraping | Prospective study (UK) | 6 | Mean=7.5 months (3 to 13 months) | 67% | NR | NR | NR | NR |
| Anderson 2001[59] USA | AMT | Case series | 15 | Mean=25.8 months (SD 2.5 months) | Unclear | NR | NR | * | * |
| Kheirkahn 2008 [62] USA | AMT | Retrospective case review | 5 | Mean=16.8 months (SD 10.8 months) | 100% | NR | NR | * | * |
| **Conjunctival limbal autograft CLAU** | | | | | | | | | |
| Dua 2000[62] UK | CLAU | Case series | 6 | Mean=18.8 months (14 to 31 months) | 50% | 100% | 0% | 100% | 100% |
| Kenyon 1989[70] USA | CLAU | Case series | 26 | Mean=18 months (2 to 45 months) | 85% | 65% | 35% | 95% | 43% |
| Moldovan 1999[74] France | CLAU | Case series | 5 | 10 to 47 months | 100% | 100% | 0% | NR | 20% (95% CI: 4% to 63%) |
| Rao 1999[23] India | CLAU | Retrospective case study analysis | 16 | Mean=19.3 (SD 13.5 months) (3 to 45 months) | 100% | 100% | 0% | 94% (95% CI: 72% to 99%) | 69% (95% CI: 42% to 87%) |
| **Limbal epithelial stem cells allografts (CLAL, KLAL)** | | | | | | | | | |
| Eslani 2015[63] NR | KLAL | Retrospective review | 5 | N/A | 60% | NR | NR | NR | NR |
| Han 2011[65] South Korea | KLAL | Retrospective case series | 22 | 47.9 months | 32% | 90% | 10% | 33% | 27% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Holland 1996[66] USA | KLAL | Retrospective review | 21 | Mean=26.4 months (6 to 63 months) | 38% | 0% | 100% | 72% | 60% |
| Huang 2011[67] China | Lr-CLAL | Retrospective non-comparative case series | 17 | Mean=16.0 months (12 to 26 months) | 100% | 29% | 71% | NR | 100% (95% CI: 82% to 100%) |
| Ilari 2002[68] UK | KLAL | Retrospective non-comparative case series | 20 | Mean=60 months (15 to 96 months) | 40% | 85% | 15% | 21% | 44% |
| Maryuma-Hosoi 2006[72] Japan | KLAL | Retrospective case series | 78 | Mean=46.6 months | 22% | 0% | 100% | 55% (41% in ocular burns patients) | NR |
| Tsai 1994[80] Taiwan | CLAL-CD | Case reports | 16 | Mean=18.5 (SD=5.4 months) | 31% | 0% | 100% | 63% | 81% |
| Tsubota 1995[81] Japan | CLAL-CD | Case series | 9 | Mean=12.3 months (2 to 17 months) | 33% | 0% | 100% | 56% | 100% |
| **More than one procedure used (CLAU, CLAL, KLAL)** | | | | | | | | | |
| Borderie 2003[60] France | CLAU | Case series | 6 | Mean=36 months (7 to 77 months) | 100% | 100% | 0% | NR | NR |
| | KLAL | | 5 | | 100% | 0% | 100% | NR | NR |
| Burcu 2014[11] Turkey | CLAU | Retrospective analysis | 16 | Mean=77.2 months (SD=35.1) | 100% | 100% | 0% | 87.5% (95% CI: 64.0% to 96.5%)** | 56% (95% CI: 33% to 77%) For total population |
| | CLAU + Lr-CLAL | | 4 | | Not included as a comparator in the CS | | | | |
| | Lr-CLAL | | 3 | | 100% | 100% | 0% | 100% | 56% (95% CI: 33% to 77%) For total population |
| | CLAU+KLAL | | 1 | | Not included as a comparator in the CS | | | | |
| | KLAL | | 2 | | 100% | 100% | 0% | 50% | |
| Gomes 2003[27] Brazil | AMT | Prospective, non-comparative interventional case series | 4 | Mean=19 months (8 to 27 months) | Not included as a comparator in the CS | | | | |
| | CLAU+AMT | | 6 | | 100% | 100% | 0% | 83.3% (95% CI: 43.7% to 97.0%) | 87.5% (95% CI: 64.0% to 96.5%) Total population (not broken out by subgroups) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lr-CLAL | | 10 | | 100% | 0% | 100% | 60.0% (95% CI: 31.3% to 83.2%) | 87.5% (95% CI: 64.0% to 96.5%)<br>Total population (not broken out by subgroups) |
| Ivekovic 2005[69]<br>Croatia | CLAU | Case series | 6 | >1 year<br>(7 to 41 months) | 100% | 100% | 0% | CLAU: 100%<br>(95% CI: 61% to 100%) | 100%<br>(95% CI: 61% to 100%) |
| | CLAU+AMT | | 4 | | 100% | 100% | 0% | CLAU + AMT: 100% (95% CI: 51.0% to 100%) | 100%<br>(95% CI: 51.0% to 100%) |
| Meallet 2003[73]<br>USA | CLAU+AMT | Retrospective, non-comparative, interventional small case series | 5 | 22 months<br>(11 to 48 months) | 60% | 100% | 0% | 100%<br>(95% CI: 56.6% to 100.0%) | 100%<br>(95% CI: 56.6% to 100.0%) |
| Miri 2010[26]<br>UK | CLAU | Retrospective consecutive cohort study | 12 | Mean=47 months<br>(12-119 months) | 50% total population | 100% | 0% | 100% | 100% |
| | Lr-CLAL | | 9 | Mean=32.6 months<br>(13 to 96 months) | | 0% | 100% | 89% | 89% |
| | CLAL-CD | | 6 | Mean=28.1 months (SD=36.9)<br>(22 to 96 months) | | 0% | 100% | 33% | 33% |
| Solomon 2002[77]<br>USA | KLAL+AMT | Retrospective non-comparative case series | 31 | Mean=34 months<br>(12 to 117.6) | 41% | NR | NR | NR | NR |
| Tan 1996[78]<br>UK | Lr-CLAL/CLAL-CD | Case series | 9 | 14.7 months<br>(4 to 24 months) | 11% | 0% | 100% | 78% | 44% |
| | CLAU | | 9 | 27.1 months<br>(10 weeks to 46 months) | 33% | 100% | 0% | 100% | 55% |
| Titiyal 2015[49]<br>India | Lr-CLAL | Open label randomised study | 10 | 6 to 22 months | 100% | 100% | 0% | 100%<br>(95% CI: 84% to 100%) | 80% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | KLAL | | 10 | 6 to 12 months | 100% | 100% | 0% | 100%<br>(95% CI: 84% to 100%) | 50% |
| Torres 2008[79]<br>Spain | CLAU | Case series | 58 | 20.8 months<br>(3 to 115 months) | 21% | 100% | 0% | 81% | NR |
| | CLAL-CD | | 14 | | 43% | 0% | 100% | 7% | NR |

AMT=amniotic membrane transplant; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; CLAL-CD= conjunctival limbal allograft from a cadaveric donor; KLAL=keratolimbal allograft; Lr-CLAL=conjunctival limbal allograft from a living relative; NR=not reported; SD=standard; VA=visual acuity
* studies excluded from Table 14 of CS due to formatting error
* * An additional 5 patients underwent CLAU + lr-CLAL (n=4) and CLAU + KLAL (n=1). In these cases the initial CLAU procedure failed and a second transplant was required. With these cases taken into account, OS is achieved in 66.7%
Source: CS, Table 12 and Table 14 (The ERG has not included the 2 review papers[64,75] cited in Table 12 of the CS)

The company summarises the studies identified in the systematic review of comparator studies for CLAU, CLAL and KLAL (CS, p134) as follows:

- There is a greater body of published evidence for the use of CLAU, CLAL or KLAL than for conservative management, but this is also largely based on case series data and is very heterogeneous in terms of patient populations (causes of LSCD and degree of severity of LSCD at baseline). Most studies included patients with a range of causes of LSCD.
- In the majority of cases, unilateral LSCD was managed with CLAU;[11,23,26,27,60,62,69,70,73,74,78,79] in some case series studies[11,49,65,68] unilateral LSCD was treated with CLAL or KLAL.
- In all but one case, bilateral LSCD was treated with CLAL or KLAL.[26,27,60,65-68,72,78-81] One study[70] described the use of CLAU in in patients with bilateral LSCD; however, at the time of the study, the use of CLAU in patients with bilateral LSCD was considered experimental. Expert opinion to the company clearly indicates that CLAU is not used in the UK NHS to treat patients with bilateral LSCD and has not been undertaken in the UK by the experts consulted. The ERG agrees with the clinical advice given to the company that CLAU is not used in the UK NHS to treat bilateral LSCD.[21,51]
- In some case series studies, the authors did not report whether the patients had unilateral or bilateral LSCD.[63,77]
- There was a range of primary clinical outcomes reported, e.g. histology (epithelialisation), VA, ocular surface outcomes, symptom improvement (pain, inflammation etc.), neo-vascularisation and rejection (allograft). There is no single universally accepted standard endpoint for assessing clinical outcomes in LSCD.
- In some cases clinical outcomes were reported on an individual patient basis or else grouped rather than stratified by cause of LSCD. Due to the design of the case series and the small patient numbers, there was limited statistical analysis or the statistical analysis was not relevant to the endpoints of interest in this review.
- In some case series there was more than one intervention non-comparatively assessed (CLAU, CLAL, KLAL, CLAU+AMT, CLAL+AMT, CLAU/CLAL/KLAL followed by keratoplasty and finally CLAU+CLAL and CLAU+KLAL).
- The impact of treatment on HRQoL was not assessed in any of the studies identified in the systematic review.

The company also reports (CS, p116) that there was variation in the duration of follow-up between studies. For CLAU and CLAL/KLAL, follow-up ranged from a mean of 12 months[69,81] to 9.4 years.[66] The ERG agrees with the company that there is considerable variation in the mean duration of follow-up; however, the ERG considers that the maximum mean length of follow-up is 77.2 months (not 9.4 years).[11]

The company cautions (CS, p112) that the results of the studies included in the systematic review of comparator technologies should be interpreted with caution due to the weak study designs and the heterogeneity in patient populations and interventions. The company discusses (Table 14) issues relevant to the studies including the patient populations, surgical technique and clinical endpoints in the included studies. The ERG agrees with the company's

opinion that the results of the studies identified in the systematic review should be viewed with caution.

Table 14 Company summary of identified evidence

| Company summary of literature |
|---|
| The internal validity of the studies for CLAU, CLAL and KLAL is compromised in several ways. There is no accepted standard endpoint to determine success or failure of the procedure and no agreement regarding the time point at which this is measured. Consequently, the endpoints used in the studies of CLAU, CLAL and KLAL are different from case series to case series. Assessment bias may further compromise the internal validity of these studies. Rather than an objective measure of the true effects of the outcome being used, many of the key endpoints of the studies are subjective, e.g. success being defined in the opinion of the surgeon who performed the procedure following slit lamp examination only and without quantified impression cytology. Furthermore, the effects on VA are rarely and poorly documented, yet this is an important outcome for patients. |
| The external validity of the studies for CLAU, CLAL and KLAL is additionally compromised. In many cases, inclusion/exclusion criteria are not confined to moderate to severe LSCD due to physical or chemical burns therefore the ability to extrapolate the results to this specific population is limited. The surgical nature of the procedure also compromises external validity, i.e. different surgeons are likely to have different individual techniques and post-operative care regimens and therefore reproducibility of the reported outcomes in different treatment centres cannot be guaranteed. Reporting bias may further compromise the external validity of the evidence base for CLAU, CLAL and KLAL as it is unlikely that surgeons will be motivated to write up case series of failed surgical procedures (or indeed that this would have been published |

AE=adverse event; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; VA=visual acuity
Source: CS, p168 and p169

## *4.11 Results of the comparator studies*

The company states (CS, p159) that pooling of the comparator data was inappropriate due to the heterogeneity issues outlined in Table 14. For the outcome of VA, the company also reports that the methods of assessment differed between studies. The ERG agrees with the company that it is inappropriate to pool the data from any of the studies.

The company reports the outcomes (where available) for ocular stability and VA from studies of CLAU and CLAL/KLAL (CS, p158 and p159). The company's observations are listed here as bullet points.

### 4.11.1 Ocular stability

**CLAU**

- Of the 11 studies providing data on CLAU, only five studies were conducted exclusively in patients with ocular burns.[11,23,27,69,74] In the remaining six studies, the proportion of patients with ocular burns varied from 21% to 85%.[26,62,70,73,78,79] Separate results were not reported for ocular burn patients, although the Dua[62] and Miri[26] studies noted 100% of all patients achieved ocular stability.
- Success rates were available for four[23,27,76] of the five studies providing data on CLAU in patients with ocular burns. The success rates were 14/16 (87.5%) or 14/21 (66.7%) with cases requiring a second transplantation taken into account], 5/6 (83.3%), 15/16 (94%) and 6/6 (100%).[11,23,27,69] The ERG notes that all four studies were conducted in patients with unilateral LSCD.

**CLAL/KLAL**

- Of the 15 studies providing data on CLAL/KLAL, only four studies[11,27,49,67] were exclusively in patients with ocular burns. In the remaining 11 studies,[26,63,65,66,68,72,77-81] the proportion of patients with ocular burns varied from 11% to 60%. With the exception of Maruyama-Hosoi,[72] separate results were not reported for ocular burn patients.
- Only three of the studies[11,27,49] providing data on CLAL/KLAL were conducted exclusively in ocular burns patients and reported success rates. The success rates were 4/5 (80%), 20/20 (100%) and 6/10 (60%). Additionally, in the Maruyama-Hosoi[72] study, success was seen in 41% of the ocular burns patients. The ERG notes that two studies[11,49] were conducted in patients with unilateral LSCD (n=25) and two studies[27,72] were conducted in patients with bilateral LSCD.

### 4.11.2 Visual acuity

**CLAU**

- Of the 11 studies providing data on CLAU, only five studies[11,23,27,69,74] were conducted exclusively in patients with ocular burns. In the remaining six studies,[26,62,70,73,78,79] the proportion of patients with ocular burns varied from 21% to 85%. Of the 15 studies providing data on CLAL/KLAL, only four studies[11,27,49,67] were conducted exclusively in patients with ocular burns. In the remaining 11 studies, the proportion of patients with ocular burns varied from 11% to 60%.[11,27,49,67]
- In studies investigating CLAU exclusively in patients with moderate to severe LSCD due to ocular burns where VA was assessed, there was a broad range of VA outcomes reported (20% to 100% of patients with improvement).[11,23,27,69,74] In the four studies[23,27,69,74] providing VA data on CLAU, improvement was seen in 6/6 (100%), 9/13 (69%), 1/5 (20%), and 10/10 (100%) patients. The ERG notes that all four studies were conducted in patients with unilateral LSCD.

**CLAL/KLAL**

- Of the 15 studies providing data on CLAL/KLAL, only four studies[11,27,49,67] were exclusively conducted in patients with ocular burns. In the remaining 11 studies,[26,63,65,66,68,72,77-81] the proportion of patients with ocular burns varied from 11% to 60%.
- In studies investigating CLAL/KLAL exclusively in patients with moderate to severe LSCD due to ocular burns where VA was assessed, there was a broad range of outcomes reported (65%-100%).[27,49,67] In the three studies[27,49,67] providing VA data on CLAL/KLAL, improvement was seen in 13/20 (65%), 8/10 (80%) and 17/17 (100%) patients. The ERG notes that one study was conducted in patients with unilateral LSCD, one study was conducted in patients with bilateral LSCD and one study was conducted in a mixed patient group.

### 4.11.3 Adverse events

The company summarises the AE data available from the studies for CLAU and CLAL/KLAL (Table 15). The company states that AE data were not available from studies reporting treatment with BSC.

Table 15 Adverse events reported in studies of CLAU and KLAL

| Study | Adverse events |
|---|---|
| **CLAU** | |
| Dua 2000[62]<br>N=6 | No intraoperative complications, infection or graft failure were reported. Post-operatively keratitis occurred in 17% of patients and one patient developed filamentary keratitis along the edge of the donor site. |
| Ivekovic 2005[69]<br>N=6 CLAU<br>N=4 CLAU+AMT | No infection, limbal graft failure or slippage of tissue was reported. In this study, there were no intraoperative complications, refractive changes or corneal neo-vascularisation in any of the donor eyes. |
| Kenyon 1989[70]<br>N=26 | No intraoperative complications, infections or graft failure were reported. |
| Meallet, 2003[73]<br>N=5 CLAU+AMT | A transient epithelial defect in one eye and migration of pigmented epithelium onto the AMT-covered limbus in another eye was reported. |
| Tan, 1996[78]<br>N=9 | CLAU failure occurred in two patients (who had chronic contact lens-associated epitheliopathy). One contact lens wearer had epithelial dysplasia in the fellow eye at the previous donor site. Subclinical involvement of the fellow eye is suggested as a reason for graft failure and donor eye complications in these eyes. |
| **CLAL/KLAL** | |
| Eslani, 2015[63]<br>N=5 KLAL | Mean time to graft rejection 52 months. |
| Gomes, 2003[27]<br>N=10 Lr-CLAL | Reconstruction failed in three cases (75%) in the first 6 months and in one (25%) >1 year after the surgery. One of these three subjects in whom treatment failed in the first 6 months presented with graft necrosis on the eighth day after the surgery. The other two patients had severe dry eye with keratinisation.<br>Systemic AEs with the use of immunosuppression were not observed in any case. |
| Han, 2011[65]<br>N=22 KLAL | Graft failure in 42% (87% reversed). Raised intra-ocular pressure was reported in 33% of patients, epithelial defect in 42% of patients and symblepharon in 18% of patients. |
| Holland, 1996[66]<br>N=21 KLAL | 54% rejection. |
| Huang, 2011[67]<br>N=17 Lr-CLAL | Allograft rejection in 18% of eyes. |
| Ilari, 2002[68]<br>N=20 KLAL | Graft failure 46% at 1 year, 67% at 2 years and 73% at 3 years. Raised IOP was reported in 26% of patients, and corneal necrosis and microbial keratitis each in 13% of patients. |
| Maruyama-Hosoi, 2006[72]<br>N=78 KLAL | 13% rejection, 33% raised IOP, 8% infections, 4% corneal perforation and 2.5% retinal detachment. |
| Solomon, 2002[77]<br>N=31 KLAL+AMT | 10/39 eyes (25.6%) developed raised intra-ocular pressure, 14 eyes (35.9%) developed persistent epithelial defects. 3 eyes developed microbial keratitis. |
| Tan, 1996[78]<br>N=9 Lr-CLAL and CLAL-CD | A range of adverse events reported in 77.8%, including cataract, glaucoma, spastic entropion, keratitis, infection and acute rejection after stopping cyclosporine. |
| Titiyal, 2015[49]<br>N=10 Lr-CLAL<br>N=10 KLAL | There were no intraoperative complications, such as damage to muscle during symblepharon release or corneal perforation. Up to the minimum follow-up period of 6 months none of the eyes in either group developed any infection or necrosis of cornea. |
| Tsai, 1994[80]<br>N=16<br>CLAL-CD | No graft failure. |
| Tsubota, 1995[81]<br>N=9 CLAL-CD | Aphakia was reported in 56% of patients, bullous keratopathy in 67% of patients, and glaucoma and cataract each in 30% of patients. |

AE=adverse event; AMT=amniotic membrane transplantation; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; CLAL-CD=conjunctival limbal allograft from a cadaveric donor; KLAL=keratolimbal allograft; Lr-CLAL=live relative conjunctival limbal allograft

Source: CS, Table 16 and Table 17

The company sought the opinion of clinical experts[51] to ascertain the types and frequency of AEs associated with CLAU, CLAL/KLAL and BSC in clinical practice in England (CS, p163 and p164).

For CLAU, clinical advice to the company (CS, p163) is that 10% of engraftments fail and will cause persistent epithelial defect in half of the cases. Infection occurs in up to 20% of grafted eyes and in up to 5% of donor eyes. Glaucoma (secondary to the post-operative use of topical steroids) is recorded in 5-10% of patients. Between 20% and 30% of patients experience failure of their CLAU treatment (with a recurrence of LSCD) within 10 years.

For CLAL/KLAL, clinical opinion to the company (CS, p164) is that 20% of engraftments fail and will cause persistent epithelial defect in half of the failures. Infection (mainly bacterial or fungal) occurs in up to 20% of grafted eyes and in up to 5% of donor eyes for Lr-CLAL. Glaucoma (secondary to post-operative immunosuppression) is recorded in 10% of patients. All CLAL/KLAL treatments fail (with a recurrence of LSCD) within 3 to 5 years.

For BSC, clinical advice to the company is that patients are likely to experience inflammatory flare-ups and treatment failures that result in epithelial defects. Approximately 90% of patients experience one flare-up and 50% of patients experience two flare-ups annually. There are also patients who experience three flare-ups each year. Approximately 5% of patients experience microbial keratitis once each year and 10% to 20% of patients need hospital treatment for infection or persistent epithelial defect each year. Infection and persistent epithelial defect are treated in hospital for between 5 and 7 days (but length of stay can be up to 14 days). Glaucoma resulting from steroid treatment is reported in 10% of patients who are treated chronically with steroids.

### 4.11.4 Health-related quality of life

No HRQoL data are reported in any of the comparator studies.

## *4.12 Conclusions of the clinical effectiveness section*

No RCTs were identified for inclusion in this appraisal. The main evidence presented in the CS is derived from a retrospective, case series study (HLSTM01) of 104 patients with moderate to severe LSCD. The data from the HLSTM01 case series study suggest that Holoclar may be a promising treatment for this population; however the ERG notes the lack of follow-up data beyond 1 year for the majority of patients.

The company's systematic literature reviews for the clinical effectiveness of Holoclar and the clinical effectiveness of comparator technologies yielded studies that were largely retrospective and observational and included small numbers of patients. The ERG agrees with the company that whilst the HLSTM01 case series study is also retrospective and

observational, it includes substantial numbers of patients. The company has attempted to minimise several potential sources of bias, however, methodological flaws remain.

All of the patients, except one, in the HSLMT01 case series study had only one eye treated with Holoclar. The company states (CS, p12) that one of the major benefits of Holoclar is that it can be used in patients with bilateral LSCD who have at least 1-2mm$^2$ of healthy limbus in one eye. However, no clinical effectiveness evidence is presented in the CS to support the use of Holoclar to treat two eyes in a single patient.

The ERG notes that the data reported in the CS includes p-values; the authors draw statistical conclusions rather than describe summary statistics. The ERG considers that by reporting the p-values and performing hypothesis testing, the company is suggesting that treatment with Holoclar is successful in a group of patients when the purpose of the case series study was descriptive only.

The company's systematic review of comparator treatments identified one randomised study[49] of CLAL versus KLAL in 20 patients with unilateral LSCD. The remaining studies reported the use of CLAU, CLAL or KLAL in case studies, case series studies, or retrospective cohort studies. The company said it was inappropriate to pool the data from any of the identified studies due to differences in patient populations, surgical techniques and reporting of outcomes. The ERG agrees that any pooling of data from the comparator studies is inappropriate.

There are no HRQoL data available for Holoclar or for any of the comparators. This means that the HRQoL benefits of treatment with Holoclar, and whether there are more HRQoL benefits with Holoclar compared with the comparator treatments, are unknown.

# 5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of Holoclar for the treatment of moderate to severe LSCD due to ocular burns.

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided electronic versions of the economic models, which were developed in Microsoft Excel.

## *5.1 ERG comment on company review of cost effectiveness evidence*

A systematic review was conducted to summarise findings from published cost effectiveness studies that are relevant to the decision problem. Full details of the strategies used to locate cost effectiveness evidence were reported in Section 5.1 and Appendix 4 of the CS. This search included indication terms, population terms and a cost effectiveness search filter. The cost effectiveness searches were date limited from January 1989 to January 2016; the searches were carried out in January 2016. The company searched the following databases: Embase, Medline (through PubMed), Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials and Cochrane Methodology Register) and Econlit. The company reported results from grey literature searches of the following conference sites: American Academy of Ophthalmology (AAO), European Association for Vision and Eye Research (EVER), European Society of Ophthalmology (ESO), Investigative ophthalmology & visual science (IOVS), The Royal College Of Ophthalmologists (RCO) Annual Congress and World Congress of Ophthalmology (WCO).

### 5.1.1 Eligibility criteria used in study selection

Two reviewers independently applied the inclusion/exclusion criteria used to facilitate study selection.

Inclusion criteria:

- Published in English and non-English
- Human population
- Patients with a confirmed diagnosis of LSCD.

Exclusion criteria:

- Outside of scope, i.e. did not address the cost effectiveness of CLAU, CLAL, KLAL or Holoclar
- Studies that were conducted in paediatric patients (aged <18 years)
- No cost effectiveness data presented for CLAU, CLAL, KLAL or Holoclar.

The ERG is satisfied that these criteria are relevant to the decision problem.

### 5.1.2 Included and excluded studies

The company identified one relevant cost effectiveness analysis by Fordham[82] and this study is included in the economic literature review (see Table 16 for study details); the data are available from an abstract publication.

Table 16 Summary of published cost effectiveness studies

| Author, journal, year | Study location, design and duration | Intervention | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Fordham, Value in Health, 2015[82] | HLSTM01<br>UK, retrospective, case-series, non-randomised, non-controlled, multicentre clinical study | GPLSCD01 (n=99)<br>Conservative treatment (n=not given) | VA and symptoms (pain, burning and photophobia) to assess QoL and QALYs (cost effectiveness analysis) | 10 years | Patients under conservative treatment had between 10.29 and 17.24 QALYs, depending on LSCD severity, whereas patients treated with GPLSCD01 showed between 15.93 and 22.49 QALYs, with a total utility gain between 5.25 and 6.04 QALYs in the GPLSCD01 group, this result being already discounted by 3.0%, in compliance with NICE guidelines.<br>Due to the utility gain, GPLSCD01 would meet NICE conventional ICER thresholds (20,000 – 30,000 GBP/QALY) up to a treatment cost of 150,000 GBP. |

GPLSCD01=Holoclar; VA=visual acuity; QoL=quality of life; QALYs=quality adjusted life years; LSCD=limbal stem cell deficiency; NICE=National Institute for Health and Care Excellence; GBP=British pound
Source: CS, Table 19

### 5.1.3 Findings from the cost effectiveness review

In the cost effectiveness analysis by Fordham,[82] the group of patients modelled to receive a Holoclar transplant demonstrated a utility gain between 5.25 and 6.04 QALYs. Resource use and costs were not estimated but the authors considered that, due to the magnitude of benefit, Holoclar costs of up to £150,000 would be warranted.

[redacted]

[redacted]

## 5.2 ERG critique of the company's literature review

In summary, the ERG concludes that the company's searches were carried out to an adequate standard. The ERG considers that the searches accurately reflect the population described in the decision problem and, where relevant, the indication described in the final scope issued by NICE. The ERG is confident that no relevant references were missed.

The ERG has some reservations about the quality of the included study. It is difficult to decipher from the abstract and the company's critique, received via the clarification response, whether the methodology is robust. Given the methodological issues highlighted by the company, the ERG does not place any weight on the results presented in the abstract.

## 5.3 Summary and critique of the company's submitted economic evaluation by the ERG

### 5.3.1 Model structure

The company has submitted two models. One relates to patients with unilateral LSCD and the other to patients with bilateral LSCD. Each model comprises two parts:

1. decision tree capturing the acute treatment pathway
2. Markov model capturing the longer-term outcomes.

The company's description of the decision tree element of their model for patients with unilateral LSCD is provided in Box 2.

Box 2 Company's description of the decision tree component of the company's model for patients with unilateral LSCD

> Patients initially undergo a biopsy procedure, if this biopsy is successful they progress to implantation with HOLOCLAR. If the initial biopsy procedure is unsuccessful they undergo a second biopsy procedure, if this is successful they progress to HOLOCLAR implantation, if it is unsuccessful, they are classed as a failure and enter the Markov model in the Failure state. Following a successful biopsy, the patient undergoes HOLOCLAR implantation. If the implantation is successful, they enter

the Stable Month 1 to 12 state in the Markov model. If the implantation is unsuccessful they enter the Failure state. Each biopsy involves an associated cost and health related quality of life decrement.

Source: CS, p81

A schematic of the Markov component of the company's model for patients with unilateral LSCD is provided in the CS and reproduced in Figure 1.

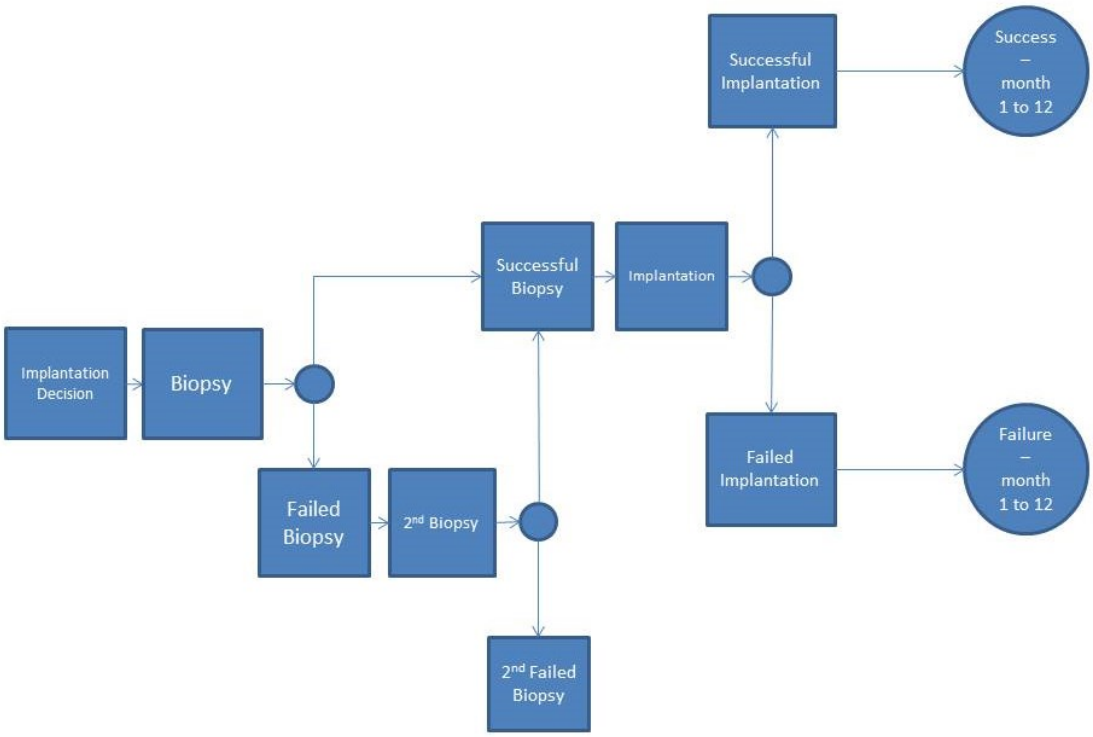



Figure 1 Schematic of the decision tree component of the company's model for patients with unilateral LSCD

Source: CS, Figure 14

A summary of the company's description of the Markov element of their model for patients with unilateral LSCD is provided in Box 3. The same model structure has been used for the intervention and the comparators except, for patients receiving CLAU, no biopsy procedure is required.

Box 3 Company's description of the pathway for patients with unilateral LSCD

If, a patient is deemed fit for an operation (see decision tree element of the model), patients enter the Markov model in either the *Stable months 1 to 12* state or the *Failure* state. Those in the *Stable months 1 to 12* state can either remain in that state or their implant may fail, in which case they move to the *Failure* state. For those who remain stable and progress to the *Stable post 12 months* state, some will be eligible for a keratoplasty at 12 months. Patients who enter the *Stable post 12 months* state will continue in this state or, at some point in the future, their HOLOCLAR implantation may fail, in which case they move to the *Failure* state. Patients in the *Failure* state will remain there for 1 year, at which point they either enter a second acute HOLOCLAR treatment pathway (captured by re-entering the decision tree) or they move to the *Best supportive care* state. Following a second

HOLOCLAR acute treatment pathway, the possible states are the same as for the initial pathway. Patients can undergo a maximum of three acute treatment pathways. Patients in all states may die.

Source: CS, p182

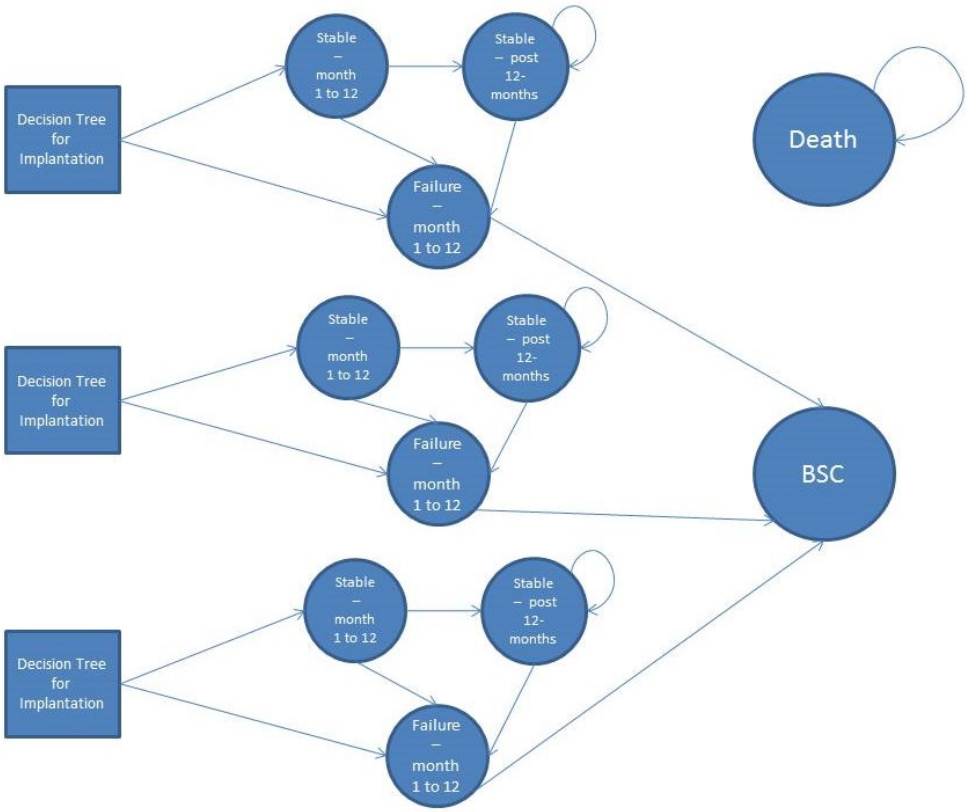



Figure 2 Schematic of the Markov component of the company's model for patients with bilateral LSCD

Source: CS, Figure 15

The model for patients with bilateral disease is the same as the model for unilateral disease with the additional complication that two eyes are being treated. It has been assumed that there would be a delay between treatments of 1 year and, therefore, for the second eye, an additional (first) year without treatment has been included.

### 5.3.2 Population

The company considers that patients participating in the HLSTM01 case series study are representative of the population described in the final scope issued by NICE, i.e. adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1 to 2mm$^2$ of undamaged limbus.

The population in the model is limited to males with a mean age of 46 years and a VA score of 10.

### 5.3.3 Interventions and comparators

There is no standard treatment for patients with severe to moderate LSCD in the NHS. This appraisal considers the comparison of Holoclar, an ex vivo expanded autologous human corneal eithelial cell transplant containing stem cells, with:

- conjunctival-limbal autograft (CLAU)
- limbal epithelial stem cells allografts:
    - living-related conjunctival allograft (Lr-CLAL)
    - keratolimbal allogeneic transplantation (KLAL)
- Best supportive care (BSC).

Holoclar is implemented within the company models in line with the EMA's marketing authorisation.[13]

The models also include a keratoplasty procedure for patients 1 year after a successful Holoclar transplant. One of the secondary outcomes of the HLSTM01 case series study is the number of successful keratoplasties after the transplant; the company states that a successful transplant can provide improvements to the ocular surface that enable a keratoplasty procedure to be undertaken.

### 5.3.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PPS). However, it should be noted that the models do not include any PPS costs. The time horizon is set at 50 years and, in the base case, both costs and outcomes are discounted at a rate of 1.5%. The company explains that a rate of 1.5% has been used as the technology has a prolonged effect and can return patients to a high utility state.

### 5.3.5 Treatment effectiveness and extrapolation

The company states a successful transplant restores a stable cornea with little or no defects or blood vessels in the cornea. Stromal scarring is the second key clinical parameter. The probability of a successful transplant with each of the comparator interventions is sourced from the literature (pooled data), while the evidence for Holoclar comes from analysis of the HLSTM01 case series study data.

There is no direct evidence of the HRQoL associated with a cornea in good condition with or without stromal scarring. The company has therefore conducted regression modelling to estimate the relationship between the appearance of the cornea and stromal scarring with (i) VA and (ii) pain, burning and photophobia.

**The relationship between transplant success, stromal scarring and visual acuity**

The company examined a number of different modelling specifications and chose a random effects ordered logistic regression model to estimate the relationship between VA, transplant success and stromal scarring. The dependent variable is generated by converting VA onto a 13-point scale from Light Perception (LP) to 10/10 Best Corrected Visual Acuity (BCVA). The model chosen by the company assumes that the relationship between VA and transplant success is the same as that observed in the HLSTM01 case series study at 12 months and that this relationship remains constant over time.

The company models assume that the relationship between a successful transplant and VA, generated from an analysis of Holoclar data, is the same regardless of the treatment.

On the basis of an eye-level random effects parameter that demonstrates a large variation in underlying VA, the company models three different baseline levels of VA: average, good and poor. Good is defined as being in the top 25% of the estimated random effects and poor in the bottom 25% and then relevant proportioned distribution mean values are given to these groups. The intercept values for poor/average/good underlying VA are -2.3/0/2.3 respectively.

The CS (Tables 23 to 25) shows the probability of each VA level, calculated from the regression coefficients, for six distinct groups: patients with and without stromal scarring at baseline, people in whom the transplant fails (with and without stromal scarring) and people whose transplant is a success (with and without stromal scarring).

**The relationship between pain/burning/photophobia and successful transplantation and stromal scarring**

Pain, burning and photophobia are identified as symptoms that have a negative impact on HRQoL. Patients in the HLSTM01 case series study self-reported the presence and severity of each of these symptoms by choosing from one of four categories (i.e., none/mild/moderate/severe) at each examination.

The company combines the data from all observations of the pain/burning/photophobia symptoms by taking the highest result overall for each patient and creating an ‘any’ category for use as the dependent variable in the regression analysis.

In the regression model, the eye-level random effects parameter used by the company demonstrated less heterogeneity for pain/burning/photophobia than for VA; the company therefore models pain/burning/photophobia for the average patient only. The probability of reporting symptoms at different levels of severity at baseline and following transplant success or failure, and depending on the presence of stromal scarring, is shown in Table 17.

Table 17 Predicted probabilities of pain/burning/photophobia

| | Baseline with SS | | Baseline w/o SS | | Transplant failure with SS | | Transplant failure w/o SS | | Transplant success with SS | | Transplant success w/o SS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XB | 2.7899 | | 1.7497 | | 1.8479 | | 0.8077 | | 1.0402 | | 0 | |
| Pain/burning/photophobia | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** |
| None | 57.47% | 57.47% | 79.27% | 79.27% | 77.61% | 77.61% | 90.75% | 90.75% | 88.60% | 88.60% | 95.65% | 95.65% |
| Mild | 85.95% | 28.47% | 94.54% | 15.27% | 94.01% | 16.40% | 97.80% | 7.05% | 97.24% | 8.63% | 99.01% | 3.35% |
| Moderate | 99.44% | 13.49% | 99.80% | 5.26% | 99.78% | 5.77% | 99.92% | 2.13% | 99.90% | 2.67% | 99.97% | 0.96% |
| Severe | 100.00% | 0.56% | 100.00% | 0.20% | 100.00 % | 0.22% | 100.00% | 0.08% | 100.00% | 0.10% | 100.00% | 0.03% |

SS=stromal scarring; XB=linear prediction of fitted model; Cum=cumulative; Prob=probability
Source: CS, Table 30

**The relationship between transplant success, keratoplasties and stromal scarring**

The probability of stromal scarring from the HLSTM01 dataset is used to indirectly estimate the impact that keratoplasty has on VA. The probability of stromal scarring at different points in the pathway is estimated from the outputs of a random effects logistic regression and shown in Table 18.

Table 18 Predicted probabilities of stromal scarring

| | Baseline | Failed transplant | Successful transplant | Successful transplant plus successful keratoplasty |
|---|---|---|---|---|
| XB | -2.2404 | -2.08286 | -2.0441 | 1.4884 |
| No stromal scarring | 9.62% | 11.08% | 11.46% | 81.58% |
| Stromal scarring | 90.38% | 88.92% | 88.54% | 18.42% |

XB=linear prediction of fitted model
Source: CS, Table 34

**Relationship between underling eye heterogeneity and length of follow-up**

The company performed regression analysis to test whether the dataset from HLSTM01 was biased and checked whether longer follow-up occurred in patients with healthier or more favourable eyes; the company concludes that this is not the case.

### 5.3.6 Health-related quality of life

The relationship between utility and level of VA, in one eye or both eyes is unclear. A systematic literature review undertaken by the company revealed no studies reporting utility scores relating to LSCD. Findings did, however, suggest that utility or utility decrements may be driven by:

- loss of VA
- pain/burning/photophobia
- a cosmetic disfigurement.

The company has undertaken two broad approaches to identify utility values to use in the models, namely:

1. a bespoke standard gamble (SG) stated preference exercise (520 members of the public)
2. the burden of disease systematic review undertaken by the company identified key symptoms that drive the overall utility of patients with LSCD (VA), pain, burning, photophobia and disfigurement). A search of broader literature was conducted to identify disutility values associated with these utility drivers.

Pain is a probabilistic function of health states, disfigurement is assumed to be present in all states except for those patients who are in a stable condition and do not have stromal scarring.

A summary of the utility values used in the company's base case analysis is displayed in Table 19.

Table 19 Summary of utilities associated with the different Markov model health states

| State | VA based utility | Pain/burning/ photophobia | Disfigurement | Overall utility |
|---|---|---|---|---|
| Baseline with stromal scarring | 0.56 | -0.019 | -0.318 | 0.223 |
| Baseline without stromal scarring | 0.60 | -0.007 | -0.318 | 0.275 |
| Transplant failure/ BSC with stromal scarring | 0.57 | -0.008 | -0.318 | 0.244 |
| Transplant failure/ BSC without stromal scarring | 0.63 | -0.003 | -0.318 | 0.309 |
| Transplant success – stable with stromal scarring | 0.60 | -0.004 | -0.318 | 0.278 |
| Transplant success – stable without stromal scarring | 0.67 | -0.001 | - | 0.669 |
| Death | 0 | - | - | 0 |

BSC=best supportive care; VA=visual acuity
Source: CS, Table 48

**Adverse events**

The company identified that reports of AEs from observational studies (CS, Section 4.12) are inconsistent and incomplete thus deriving absolute and relative risk values was not possible. The company, therefore, sought advice from clinical experts.[51] The glaucoma rates used in the company models are displayed in Table 20.

Table 20 Glaucoma rates used in the company models

| Procedure | Rate | Source |
|---|---|---|
| CLAU | 5% | Expert opinion[51] |
| Lr-CLAL | 10% | Expert opinion[51] |
| KLAL | 10% | Expert opinion[51] |
| Holoclar | 3.5% | SmPC[30] |

CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; SmPC=summary of product characteristics
Source: Submitted economic models

### 5.3.7 Resources and costs

The company presents the procedural resource use and costs in two sections: those relating to the initial biopsy (Table 21) and those associated with the main transplant (Table 22). The ERG identified some minor discrepancies between the values used in the CS and the values used within the models.

## Extraction biopsy

Table 21 Resource use and costs for cell extraction biopsy

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| Minor eye procedure | £675.73 | Holoclar | 1 | NHS Reference Cost: Minor, Cornea or Sclera Procedure for Extraction[83] |
| | | CLAU | 0 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 0 | |
| Amniotic membrane | £[redacted] | Holoclar | 0 | Frozen amniotic membrane 2x2cm NHS Blood and Transport |
| | | CLAU | 1 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 2 | |
| Bandage contact lens applied by an ophthalmologist | £4.17 | CLAU only | 1 | http://www.visiondirect.co.uk/purevision |
| Outpatient appointment | £60.13 | Holoclar | 1 | NHS Reference Cost: Average cost of a medical ophthalmology outpatient appointment[83] |
| | | CLAU | 0 | |
| | | Lr-CLAL | 5 | |
| | | KLAL | 0 | |
| Antibiotic eye drops | £0.007 | All | 4 x day, 3 weeks | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| Steroid eye drops | £0.01 | All | 4 x day, 3 weeks | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2- 100 |
| Artificial tears | £0.037 | All | 4 x day, 3 weeks | MIMs Online[84] Carmellose Sodium 0.5% 10mL |

CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft
Source: Submitted economic models

## Main transplant

Table 22 Resource use and costs for cell implantation

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| Holoclar | £[redacted] | Intervention-specific costs | 1 | CS |
| CLAU | £0 | | 1 | |
| Ir-CLAL | £0 | | 1 | |
| KLAL | £[redacted] | | 1 | Single Cornea- NHS Blood and Transplant |
| Surgery | £2,934.30 | All | | NHS Reference Cost: Very Complex, Cornea or Sclera Procedures with CC Score 0-1[83] |
| Amniotic membrane | £[redacted] | Holoclar | 0 | Frozen amniotic membrane 2x2cm NHS Blood and Transport |
| | | CLAU | 1 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 2 | |

CS=company submission; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft
Source: Submitted economic models

## Health state resource use and costs

The resource use assumed for post-transplant health states in the models are described in Table 23.

Table 23 Resource use and costs in modelled health states

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| **Stable first 12 months** | | | | |
| Antibiotic eye drops | £0.007 | Holoclar | 0 | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months | |
| Steroid eye drops | £0.01 | Holoclar | 0 | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2 - 100 drops |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months | |
| Artificial tears | £0.037 | Holoclar | 0 | MIMs Online[84] Carmellose Sodium 0.5% 10mL |
| | | CLAU/Lr-CLAL, KLAL | 4 x day, first 3 months | |
| Autologous serum eye drops | £[redacted] | Holoclar | 0 | NHS Blood and Transplant |
| | | CLAU/Lr-CLAL, KLAL | 2 | |
| Outpatient appointments* | £60.13 | Holoclar | 5 | NHS Reference Cost: Average cost of a medical ophthalmology OP appointment[83] |
| | | CLAU/Lr-CLAL, KLAL | 10 | |
| Immunosuppressants** | | For 12 months for patients who received Lr-CLAL or KLAL | | |
| **Stable post-12-months:** No on-going treatment required | | | | |
| **Failure**: No cost associated with failure*** | | | | |
| **Best supportive care** | | | | |
| Regular ophthalmology outpatient appointments | £60.13 | All | 6 per year | NHS Reference Cost: Average cost of a medical OP ophthalmology appointment[83] |
| Antibiotic eye drops | £0.007 | All | 4 x day | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2- 100 drops |
| Steroid eye drops | £0.01 | All | 4 x day | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| Artificial tears | £0.037 | All | 4 x day | MIMs Online[84] Carmellose Sodium 0.5% 10mL |
| Flare-ups | | Treated with autologous serum eye drops and a course of oral antibiotics | 2 x year | |
| Autologous eye drops | £[redacted] | | | NHS Blood and Transplant |
| Oral antibiotics | £0.09 | | | MIMs Online[84] - Oral Tetracycline 28 packet £2.62 |
| **Keratoplasty** | | | | |
| Keratoplasty product | £[redacted] | All | | Single Cornea- NHS Blood and Transplant |
| Major eye procedure | £2,934.30 | All | | NHS Reference Cost: Very Complex, Cornea or Sclera Procedures with CC Score 0-1[83] |
| Outpatient appointments | £60.13 | All | 6 | NHS Reference Cost: Average cost of a medical ophthalmology OP appointment[83] |
| Antibiotic eye drops | £0.007 | All | 4 x day, 2 months | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2- 100 drops |
| Steroid eye drops | £0.01 | All | 4 x day, 2 months | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| Artificial tears | £0.037 | All | 4 x day, 2 months | MIMs Online[84] Carmellose Sodium 0.5% 10mL |

CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; OP=outpatient
Source: CS, Section 5.5 and company models
*The CS states, weekly for first 2 months, fortnightly from 3– 6 months and then monthly up to 12 months (i.e. 22 appointments)
** The costs of immunosuppressants are not included within the models
***The first 12 months post-transplant failure is allocated the same resource use as BSC

**Adverse event costs**

The cost in the models associated with treating glaucoma is £1,151 taken from the ERG report for aflibercept for treating diabetic macular oedema.[85]

### 5.3.8 Cost effectiveness results

Total and incremental costs and QALYs for the comparison of Holoclar with the available treatment options for unilateral and bilateral LSCD are shown in Table 24 to Table 27. In the base case, for both unilateral and bilateral disease, all treatment options are dominated by CLAU; CLAU is the most effective and cheapest treatment option of all treatments considered. When CLAU is removed from the decision-space and Holoclar is compared to the most effective alternative treatment (KLAL, in both populations), Holoclar generates additional benefits at an additional cost.

A breakdown of the proportions of patients in each health state over time, the contribution of each of the components to the total utility of each intervention and the share of total costs attributable to each treatment or BSC are shown in Tables 53 to 57 in the CS.

For clarity, the ERG also presents a pair-wise comparison of Holoclar with each of the comparator options. The results for unilateral disease are presented in

Table 25, for unilateral disease and for bilateral disease in Table 27.

Table 24 Base case results - unilateral LSCD

| | Costs | QALYs | ICER per QALY gained: each treatment versus baseline |
|---|---|---|---|
| CLAU | £22,158 | 12.64 | CLAU dominates all treatments as it is cheaper and more effective |
| Lr-CLAL | £77,434 | 9.73 | |
| KLAL | £89,256 | 9.80 | |
| Holoclar | £[redacted] | 12.09 | |
| BSC | £101,535 | 7.18 | |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: CS, Table 51

Table 25 Base case results - unilateral LSCD (pair-wise comparisons with Holoclar)

| | Incremental costs | Incremental QALYs | ICER per QALY gained: Holoclar vs comparator |
|---|---|---|---|
| Holoclar | - | - | - |
| CLAU | -£72,264 | 0.55 | Holoclar is dominated by CLAU; Holoclar is more expensive and less effective |
| Lr-CLAL | -£16,988 | -2.36 | £7,185 |
| KLAL | - £5,167 | -2.29 | £2,255 |
| BSC | £7,112 | -4.91 | Holoclar dominates BSC: Holoclar is cheaper and more effective |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Adapted from CS, Table 51

Table 26 Base case results - bilateral LSCD

| | Costs | QALYs | ICER per QALY gained: treatment versus baseline |
|---|---|---|---|
| CLAU | £47,402 | 10.08 | CLAU dominates all treatments as it is cheaper and more effective |
| Lr-CLAL | £155,430 | 6.36 | |
| KLAL | £173,844 | 6.56 | |
| HOLOCLAR | £[redacted] | 9.25 | |
| BSC | £193,323 | 2.44 | |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: CS, Table 52

Table 27 Base case results - bilateral LSCD (pair-wise comparisons with Holoclar)

| | Incremental costs | Incremental QALYs | ICER per QALY gained: Holoclar versus comparator |
|---|---|---|---|
| Holoclar | - | - | - |
| CLAU | -£144,014 | 0.83 | Holoclar is dominated by CLAU; Holoclar is more expensive and less effective |
| Lr-CLAL | -£35,986 | -2.89 | £12,438 |
| KLAL | - £17,572 | -2.69 | £6,533 |
| BSC | £1,906 | -6.81 | Holoclar dominates BSC; Holoclar is cheaper and more effective |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Adapted from CS, Table 52

### 5.3.9 Sensitivity analyses

**Deterministic sensitivity analysis**

The company presents a number of scenario analyses based on changes to some key assumptions in the models. The parameters varied include the discount rate, the utility value for disfigurement, the success of comparative surgical interventions and the timeframe over

which cost effectiveness is assessed in the models. The ICERs for each scenario are presented in Table 28 for unilateral disease and in

Table 29 for bilateral disease.

Table 28 Sensitivity analysis - unilateral LSCD (pair-wise comparisons with Holoclar)

| | ICER per QALY gained | | | |
|---|---|---|---|---|
| **Scenario** | **CLAU** | **Lr-CLAL** | **KLAL** | **BSC** |
| Base case | Holoclar is dominated | £7,185 | £2,255 | Holoclar dominates |
| 3.5% discount rates | Holoclar is dominated | £21,182 | £15,245 | £3,563 |
| No disfigurement utility decrement | Holoclar is dominated | £35,076 | £11,546 | Holoclar dominates |
| 3.5% discount rates, no disfigurement disutility decrement & 4 flares per year in BSC | Holoclar is dominated | £25,164 | £7,586 | Holoclar dominates |
| No disfigurement decrement, CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates | £488,615 | £487 | £9,138 | Holoclar dominates |
| *CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates and 22 year time horizon | £167,201 | £13,651 | £29,488 | £5,743 |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Submitted economic models
*Costs in the model are slightly different to the costs reported in the submission

Table 29 Sensitivity analysis - bilateral LSCD (pair-wise comparisons with Holoclar)

| | ICER per QALY gained | | | |
|---|---|---|---|---|
| **Scenario** | **CLAU** | **Lr-CLAL** | **KLAL** | **BSC** |
| Base case | Dominates | £12,438 | £6,533 | Dominated |
| 3.5% discount rates | Dominates | £34,817 | £29,818 | £6,708 |
| No disfigurement utility decrement | Dominates | £31,850 | £21,861 | Dominated |
| 3.5% discount rates, no disfigurement disutility decrement & 4 flares a year in BSC | Dominates | £26,384 | £39,595 | Dominated |
| No disfigurement decrement, CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates | £486,145 | £1,928 | £19,049 | Dominated |
| CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates and 28 year time horizon | £255,563 | £11,368 | £27,898 | £5,060 |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Submitted economic models

**Probabilistic sensitivity analysis**

The company states (CS, p232) that the PSA generates cost effectiveness acceptability curves that suggest there is a 100% likelihood of CLAU being the most cost effective option.

### 5.3.10 Model validation and face validity check

The company reports that their estimates of distributions of VA states, presence of stromal scarring and pain/burning/photophobia were validated against the HLSTM01 dataset.

The company states that external validation of the costs and HRQoL of people with LSCD is not possible due to a paucity of evidence. The company highlights that (i) mapping from best seeing eye to utility is well established and (ii) utility decrements due to pain are based on established EQ-5D tariffs.

The company states the authors of the SG study conducted by the York Health Economics Consortium (YHEC) for the company (CS, Appendix 7) estimate a large utility decrement for disfigurement, which is consistent with the opinion of clinical experts.

### 5.3.11 NICE reference case checklist

Table 30 NICE Reference case checklist completed by ERG

| Attribute | Reference case | Does the de novo economic evaluation match the reference case? |
|---|---|---|
| Decision problem | The scope developed by NICE | Yes |
| Comparator(s) | As listed in the scope developed by NICE | Yes. Both unilateral and bilateral are compared with conjunctival limbal autograft (CLAU), limbal epithelial stem cells allografts (Lr-CLAL and KLAL) and BSC |
| Perspective costs | All direct health effects, whether for patients or, when relevant, carers | Yes |
| Perspective benefits | NHS and PSS | Partial - patient related direct health effects are considered. No impact on carers has been considered in the models |
| Form of economic evaluation | Cost utility analysis with fully incremental analysis | Yes |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Yes |
| Synthesis of evidence on outcomes | Based on systematic review | No. Only case series data are available for Holoclar. The company carried out a systematic review of evidence for comparator interventions. The company pooled outcome data from the review and used the pooled estimates in the submitted models. The ERG notes that heterogeneity in populations and study designs add considerable uncertainty to these pooled estimates |
| Outcome measure | Health effects should be expressed in QALYs. | Yes |
| Health states for QALY | Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults | Yes, indirectly. Utility values were mapped using data from VA studies to EQ-5D values. Symptomatic decrements to quality of life were sourced from the literature |
| Benefit valuation | Reported directly by patients and/or carers | No |
| Source of preference data for valuation of changes in HRQoL | Representative sample of the UK population | Indirectly |
| Discount rate | The same annual rate for both costs and health effects (currently 3.5%) | No. A discount rate of 1.5% for costs and benefits was used in base case. The company states that if a transplant with Holoclar is successful, then long-term benefits are achieved and patients experience high levels of utility. The ERG does not consider use of this discount rate to be valid |
| Equity | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| Sensitivity analysis | Probabilistic sensitivity analysis | The models are not fully probabilistic. Deterministic scenario analyses are presented |

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; VA=visual acuity; BSC=best supportive care

### 5.3.12 Drummond checklist

Table 31 Critical appraisal checklist for the economic analysis completed by the ERG

| Question | Critical appraisal | ERG comment |
|---|---|---|
| Was a well-defined question posed in answerable form? | Yes | |
| Was a comprehensive description of the competing alternatives given? | Yes | |
| Was the effectiveness of the programme or services established? | Yes | The data are derived from a retrospective, case series study (HLMST01) |
| Were all the important and relevant costs and consequences for each alternative identified? | Yes | Some of the assumptions in the model were unsupported by data |
| Were costs and consequences measured accurately in appropriate physical units? | Yes | |
| Were the cost and consequences valued credibly? | Yes | |
| Were costs and consequences adjusted for differential timing? | Yes | |
| Was an incremental analysis of costs and consequences of alternatives performed? | Yes | |
| Was allowance made for uncertainty in the estimates of costs and consequences? | Partial | The results of PSA are reported but many parameters lack estimates of their uncertainty, therefore the model is not fully probabilistic. Deterministic sensitivity analysis results are reported |
| Did the presentation and discussion of study results include all issues of concern to users? | Yes | |

PSA=probabilistic sensitivity analysis; ERG=Evidence Review Group

## *5.4 Detailed critique of the company's economic model*

Section 5.5.1 provides the ERG's assessment of the model structure and also the effectiveness data incorporated into the company's economic model. Sections 5.4.2 to 5.4.5 describe four issues that have a major impact on the cost effectiveness results generated by the company model (i.e., HRQoL, the discount rate, the use of autologous serum eye drops and use of KLAL on failure with Lr-CLAL).

### 5.4.1 Summary of model structure and included data

The company provided the model in MS Excel. The ERG considers that the model was reasonably well constructed with no flaws in the algorithms used to generate base case results and was straightforward to use. Some of the scenario options built into the model did not seem to function but these did not impact on the ability of the ERG to generate cost effectiveness results.

Following clinical advice, the ERG agrees with the company that CLAU is not a plausible procedure for patients with bilateral LSCD and so should not be included as a comparator.

The ERG notes the numerous data quality issues related to study design discussed in Section 4 and considers that all of the included studies in the systematic review are equally flawed. However, in contrast to the company's statement that it was inappropriate to pool the data from the comparator studies due to parameter heterogeneity, pooled estimates of the effectiveness data are used in the base case economic models. It is not clear whether this is a pooling of data from specific studies of patients with ocular burns, or is a pooling of data from all studies and all patients. However, as the individual studies have very small sample sizes, the ERG considers it doubtful that selection of any one study will produce more robust results than the pooled analysis. However, the weak evidence base from which the comparator effectiveness is drawn needs to be taken into account when assessing the robustness of the ICERs generated by the company models.

Clinical advice to the company is that Lr-CLAL and KLAL procedures all fail by 5 years. However, the company models suggest that 32.2% of patients with Lr-CLAL and 24.2% of patients with KLAL have a stable first transplant at 5 years. Whilst this could mean that the success rates of Lr-CLAL and KLAL are overstated in the company models, this assumption is consistent with the published studies[11,26,27,49,51,65,66,68,72,77-81] identified in the CS, if not with clinical opinion.

Similarly, clinical advice to the company is that 30% of CLAU transplants fail by 10 years. However, the models assume that the 86.8% of patients that have successful transplants at 12 months are considered to have successful transplants for life. The same assumption is made for Holoclar patients who have stable transplants at 12 months. The models cannot be changed to allow failure rates at 10 years without completely restructuring them and this modification is beyond the remit of the ERG. In any case, the evidence to support the restructure would only be from a single clinical opinion on CLAU and there is no evidence on 10-year survival for Holoclar beyond one patient from the HLMST01 case series study. The ERG considers it an inherent weakness in the models that longer term (post-12 months) failure rates cannot be explored. If transplant failure occurs post 12 months for CLAU and Holoclar, then the ICERs per QALY gained for both treatments compared to the alternative procedures would increase. The impact on the ICER per QALY gained between Holoclar and CLAU of failure post 12 months would be dependent on the relative failure rate between the two procedures, which is unknown.

The ERG requested patient level data from the HLMST01 case series study that was used to generate the clinical effectiveness results for Holoclar. The ERG considers that a simpler analysis of the data could have been performed than was carried out by the company. The company could have looked at the success rate associated with removing disfigurement and the average line increase in VA – especially given that improvement in VA was arbitrarily

grouped into the worst 25%, middle 50% and best 25% of eyes in any case. The ERG did not reproduce the logistic regressions the company undertook to generate effectiveness results. However, by checking baseline VA, stromal scarring and simple effectiveness rates, the ERG is confident that the results generated from the company's regressions and analysis of the HLMST01 dataset, and incorporated into the models, are satisfactory.

There are significant issues relating to the absence of clinical effectiveness data to support the use of Holoclar to treat both eyes in patients with bilateral LSCD and these are discussed in detail in Section 3. Due to this absence of supporting evidence, the ERG considers that, whilst the ERG modifications described in the rest of this section for bilateral model results are presented, they should be interpreted as the results of a 'what if' scenario rather than the results of a robust analysis.

### 5.4.2 Health-related quality of life

Whilst the company has made a laudable attempt to estimate utility values in a patient population for which no utility values are available, the ERG considers that the utility values associated with the different health states employed in the base case models are implausibly low. In the company's unilateral model, the health state of transplant success and keratoplasty for patients with pre-operation 'good' eyesight in the worst seeing eye has the highest utility value of 0.706 (0.692 in the bilateral model). All other states with transplant failure or BSC have a utility value below 0.360 (e.g., the utility value is as low as 0.04 for patients with poor vision and stromal scarring in the bilateral model).

For perspective, a utility value of 0.360 is lower than the utility value reported for patients with various cancers receiving palliative treatment only in the last 3 months of life.[86] These utility values are all also significantly lower than the utility values employed in other modelling work undertaken by NICE in eye-related diseases. For example, in the chronic open angle glaucoma guideline,[87] the utility values used in the model were all above 0.819 except for severe visual impairment where a base case value of 0.503 was used; in this model, the lower limit for severe visual impairment was 0.331 and this is the only value that is at all commensurate with the lower values employed in the company model. Whilst it is reported in the CS (p67) that patients may have multiple co-morbidities related to the incident resulting in LSCD that could reduce a person's HRQoL to the utility levels employed in the model, the CS and model are only concerned with utility values associated with the eye and treatment of LSCD. In the absence of utility values directly for this population, the assumption has to be made (which the company has rightly done) that the utility values reflect otherwise healthy patients only with utility decrements related to the LSCD.

The ERG considers that more appropriate utility values should be chosen to produce more realistic ICERs accepting that there is no utility set specifically for the population being modelled. There are two factors that drive the company's low utility values and, for each of these factors, alternative values can be used.

The first is the choice of VA utility values used in the company model. Using the Czoski-Murray (2009)[88] approach (Time Trade Off methodology and patients with wet age-related macular degeneration) coupled with an adjustment based on data from Finger[89] yields a maximum utility value of 0.706 assuming vision of 0.6 to 1.0 in both eyes and this utility value is used in the unilateral base case model. This value is lower than the utility value of 0.856, assuming perfect vision in both eyes, that is estimated when using the Czoski-Murray approach as described in the aflibercept STA[90] and is lower than the UK population norm of 0.840 for full health in a male patient aged 46[91] - the representative patient in the company model.

The reason for the difference in utility values from the Czoski-Murray approach[88] in the CS and the aflibercept STA[90] is not easy to determine from the information provided by the company. Whatever the underlying cause, the ERG considers that the utility values used in the model must be reflective of reality. As the maximum and minimum utilities generated by the company's approach are implausible, both compared to the population norm and to the values used in other eye disease modelling for previous submissions, an alternative method that produces higher VA utilities is preferable.

As there are no EQ-5D utility values available for VA in patients with moderate to severe LSCD due to ocular burns, the ERG carried out a non-systematic search for other potential VA utility values focussing on previous NICE guidelines and STAs in eye disease. The results of the search revealed that there are no better alternatives than those considered by the company. The ERG then considered all of the utility value options available in both the unilateral and bilateral models on the basis of the plausibility of the upper and lower values of the health states described in the company model (Table 32).

Table 32 Utility values generated by the company model for highest and lowest utility health states using different VA utility sources

| | VA utility source | | | |
|---|---|---|---|---|
| | Czoski-Murray group means (2009)[88] (Base case) | Brown (2003)[92] | Brown (2008)[93] | Czoski-Murray OLS model (2009)[88] |
| Highest utility value health state in economic models (unilateral, good prior vision and successful transplant and keratoplasty) | 0.706 | 0.861 | 0.920 | 0.799 |
| Lowest utility value in economic models (bilateral, poor prior vision and unsuccessful transplant with stromal scarring) | 0.04 | 0.285 | 0.07 | -0.208 |

OLS=Ordinary Least Squares; VA=visual acuity
Source: adapted from CS, Table 43 and company model

The values in Table 32 are the results generated by the company model. As shown in Table 32, the lower bound utility values are implausible for all but those generated from the Brown 2003 values.[92] Even though the lower bound is lower than values reported in other eye disease related STAs and guidelines, such as the chronic open angle glaucoma guideline,[87] the upper bound is in line with the 0.840 UK population norm for the reference patient entering the model. Arguments can be made for and against the methodology used in any of the studies considered in Table 32 but the ERG considers that plausibility of results has to be the deciding factor and the most plausible values are generated from Brown 2003.[92]

Using the Brown 2003[92] utility values decreases the QALY gain from Holoclar in the unilateral case from 2.36 to 2.24 versus Lr-CLAL with the ICER increasing to £7,576 per QALY gained. Versus KLAL, QALY gain is reduced from 2.29 to 2.18 with the ICER increasing to £2,367 per QALY gained. Versus BSC, QALY gain is reduced from 4.91 to 4.33, with Holoclar still dominating BSC. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreased from 0.55 to 0.52.

In the bilateral case, QALYs decreased from 2.89 to 2.59 versus Lr-CLAL with the ICER increasing to £13,916 per QALY gained. Versus KLAL, QALY gain is reduced from 2.69 to 2.34 with the ICER increasing to £7,512 per QALY gained. Versus BSC, QALY gain is reduced from 6.81 to 5.33, with Holoclar still dominating BSC. There is no comparison of Holoclar versus CLAU.

The second reason for the low utility values is the 0.318 decrement applied for disfigurement in any eye to all patients that do not have a successful keratoplasty. The decrement is applied equally regardless of the extent of disfigurement and is derived from the SG study conducted by the York Health Economics Consortium (YHEC) for the company (CS, Appendix 7).

Compared to KLAL and Lr-CLAL, the ERG calculated that 80% of the QALY gain generated in the company unilateral model base case from Holoclar arises from the removal of disfigurement, so not only is it important to obtain a robust value for disfigurement to generate plausible overall utility values, it is also important as it is the biggest driver of QALY gains in the company's model.

The company is rightly cautious about using the results of the SG study and notes several contradictory values that suggest that the individuals who participated in the study did not fully understand the questions being asked. However, the company uses a utility value for disfigurement in their base case unilateral and bilateral models that is drawn from a regression analysis of the findings from this same SG study. The company's regression analysis does not (and cannot) rectify the underlying data quality issues in the SG study and so the value used in the company model is no more robust than any of the values drawn directly from the SG study.

The company has also assumed that the disfigurement utility is the same regardless of a patient's level of corneal opacity, corneal neovascularisation and inflammation. The ERG notes there was a distribution of these parameters in the baseline population of the HMST01 case series study. The ERG considers that it is likely that patients therefore have a range of severity of disfigurement. Essentially the same disutility is applied in the company models whether a patient has just one affected eye with inflammation or both eyes have severe corneal opacity, corneal neovascularisation and inflammation. Application of just one disutility value for disfigurement – especially one so high – does not therefore accurately measure the impact of disfigurement in this population.

The ERG conducted a non-systematic review of the literature and found no utility values for eye disfigurement other than that for cataracts from the aflibercept STA.[90,94] For comparison, the decrement of 0.318 is greater than that reported by the authors of a review of utility values for economic modelling in Type 2 diabetes for amputation of a limb (0.280) or for cataracts (0.140) as reported in the aflibercept ERG report.[90] Disfigurement is a HRQoL issue for patients with LSCD. However, as there are no robust utility values available, the actual impact on utility remains unknown but the ERG's comparison to other utility values such as amputation and cataracts suggests that the decrement applied by the company may be too high.

The ERG considers that, whilst not directly comparable to eye damage from LSCD, cataracts produce opaqueness in the eye, albeit in the lens rather than in the cornea, so utility values associated with cataracts may be a reasonable proxy for the disfigurement associated with LSCD. The utility decrement associated with cataract disfigurement is smaller than the

decrement associated with LSCD disfigurement and clinical advice was that disfigurement with LSCD can be worse than with cataracts although as stated earlier there will be a range of levels of disfigurement with LSCD. However, the decrement associated with cataracts also includes a loss of utility from both disfigurement and vision loss and so the utility decrement for cataract is already higher than just for the disfigurement alone. However, the ERG accepts clinical expert advice that disfigurement is a concern to patients with LSCD and so has used the full 0.140 decrement for cataracts to represent the disfigurement decrement for patients with LSCD in the base case model. The ERG considers that whilst this may still be an inaccurate estimate of the true disfigurement utility and is also a single disutility to cover a diverse range of potential disfigurement, it is a more appropriate choice both on the grounds of plausibility (it is in line with an eye condition that produces similar if not potentially as severe visual disfigurement) and also on robustness (it is derived from a UK population that actually experiences the condition).

Using the 0.140 utility decrement for disfigurement decreases the QALY gain from Holoclar in the unilateral case from 2.36 to 1.31 versus Lr-CLAL with the ICER increasing to £12,960 per QALY gained. Versus KLAL, the QALY gain decreases from 2.29 to 1.26 with the ICER increasing to £4,107 per QALY gained. Versus BSC, the QALY gain decreases from 4.91 to 3.10 with Holoclar still dominating BSC. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreases from 0.55 to 0.31.

In the bilateral case, QALY gain decreases from 2.89 to 1.90 versus Lr-CLAL with the ICER increasing to £18,890 per QALY gained. Versus KLAL, the QALY gain decreases from 2.69 to 1.63 with the ICER increasing to £10,762 per QALY gained. Versus BSC, the QALY gain decreases from 6.81 to 5.07 with Holoclar still dominating BSC. There is no comparison of Holoclar versus CLAU.

Applying the VA utility values and cataract utility decrement (as discussed) in the company model changes the range of utility values produced by the model from 0.463 (unilateral patient with disfigurement and poor vision) to 0.861 (unilateral patient with 0.6 to 1.0 vision in both eyes) and successful keratoplasty (essentially returned to full or almost full health). These are utilities that are in line with the population norms for the upper utility value and for the lower value in line with the worst health states in the chronic open angle glaucoma guideline.[87]

It is noted that the utility value for successful keratoplasty – whether the ERG value (0.140) or the value used in the company model (0.318) – assumes that the disfigurement disutility is only due to disfigurement that can be rectified 100% by keratoplasty. If the disfigurement disutility is related to damage around the eye socket or parts of the eye untreated by

keratoplasty, then this assumption does not hold and the utility value and QALY gain from successful transplant and keratoplasty would not be so great.

Using the Brown 2003[92] VA utility values and the 0.140 utility decrement for disfigurement decreases the QALY gain from Holoclar in the unilateral case from 2.36 to 1.19 versus Lr-CLAL with the ICER increasing to £14,291 per QALY gained. Versus KLAL, the QALY gain decreases from 2.29 to 1.15 with the ICER increasing to £4,494 per QALY gained. Versus BSC, the QALY gain decreases from 4.91 to 2.52 with Holoclar still dominating BSC. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreases from 0.55 to 0.28.

In the bilateral case, QALYs decrease from 2.89 to 1.60 versus Lr-CLAL with the ICER increasing to £22,524 per QALY gained. Versus KLAL, QALYs decrease from 2.69 to 1.28 with the ICER increasing to £13,702 per QALY gained. Versus BSC, QALYs decrease from 6.81 to 3.60 with Holoclar still dominating BSC. There is no comparison of Holoclar versus CLAU.

The company also applied a utility decrement for pain/burning/photophobia in the model using the EQ-5D norms: Level 2 pain for moderate pain and Level 3 pain for severe pain. In the absence of directly collected EQ-5D data from patients with LSCD, the ERG considers this approach to be reasonable and notes that the actual decrements applied to each health state are small and do not exceed 0.02. However, the company assumes that any pain/burning/photophobia experienced by patients is for life unless the transplant is successful. The ERG considers that this assumption is potentially implausible although accepts that the true position is unknown. To explore the importance of the pain decrement, the ERG estimated the impact on the size of the ICER per QALY gained through a scenario analysis (i.e. removal of the pain decrement) and found that it made only a very small impact on incremental QALYs of between 0.01 and 0.02 and so did not consider that this was significant enough to alter in the model.

### 5.4.3 Discount rate

The company has applied a discount rate of 1.5% pa to both costs and benefits. The Appraisal Committee may consider using a discount rate of 1.5% pa instead of the NICE standard Reference Case discount rate of 3.5% pa if the following condition from the NICE Guide to the Methods of Technology Appraisal[54] is met:

*In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be*

*considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. (Section 6.2.19)*

The ERG considers that the technology presented in this submission does not extend life or affect a cure for terminal disease and as such the first clause in the above condition does not apply.

HRQoL is impaired by moderate to severe LCSD. However, the extent of the severity is unknown. In addition, whether Holoclar, or any of the other interventions considered in this appraisal, is able to remove this impairment and result in patients being at or near full health is also unknown.

An assessment of the severity of the condition is ultimately subjective in the absence of any actual HRQoL data from patients with moderate to severe LCSD due to ocular burns. The utility evidence described in Section 5.4.2 suggests that there is a reasonable HRQoL loss particularly associated with disfigurement. On balance, the ERG considers that taking into account evidence from clinical experts, who consider that this disfigurement is severe, the loss in utility for this group of patients - even if just 0.140 as assumed in the ERG amendment – is significant and of concern to this group of patients.

The issue then is whether the procedures under consideration in this appraisal raise HRQoL back to full or near full health for this group of patients. The ERG considers this is not the case for the majority of patients with moderate to severe LSCD due to ocular burns who undergo treatment with Holoclar or any of the other procedures.

As stated in the CS, this is a patient group that often has other serious co-morbidities related to the incident that caused the LSCD. As such, even if the eye damage was fully rectified, some of these patients would not be restored to full or near full health. Even in patients that have no other co-morbidities with unilateral LSCD, the company model estimates that 76.6% have transplant success with Holoclar. Of these, 50.5% will not have stromal scarring and so will maintain the utility decrement for disfigurement. Thus, only 38.6% of all patients treated with Holoclar will have no disfigurement after treatment. Of those 38.6%, only 25% will have a ‘good’ level of VA in the operated eye with the majority of these patients having good VA in the eye before the operation. The majority of patients without disfigurement do not therefore have their vision restored beyond a poor or average level of VA (where ‘average’ is for the patient group not for the population as a whole).

Holoclar and the other procedures considered in the CS do appear to offer the hope of a return to near or full health for individuals whose only HRQoL issue is due to LSCD, which is both severe in disfigurement and in VA. However, for most individuals the procedures can only

improve HRQoL rather than come close to restoring it nearly or fully. As such, the ERG considers that the appropriate discount rate to use in the model is 3.5% pa.

Using a 3.5% pa discount rate for costs and benefits in the unilateral case increases the ICER for Holoclar versus Lr-CLAL to £21,182 per QALY gained. Versus KLAL, the ICER increases to £15,245 per QALY gained. Versus BSC, Holoclar no longer dominates and ICER is £3,563 per QALY gained. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreases from 0.55 to 0.41 and the incremental cost of Holoclar decreases to £69,491.

In the bilateral case, the ICER for Holoclar versus Lr-CLAL increases to £34,817 per QALY gained. Versus KLAL the ICER increases to £29,818 per QALY gained. Versus BSC, Holoclar no longer dominates BSC and the ICER is £6,708 per QALY gained. There is no comparison of Holoclar versus CLAU.

This is a key finding for patients with bilateral LSCD treated in both eyes with Holoclar. As stated previously, there is no argument that, if the company utility values are true, then applying a 1.5% pa discount rate to costs and benefits is inappropriate. However, under the company base case assumptions, the mean utility for a stable successful Holoclar transplant is just 0.42 which cannot be considered as 'close to full health'. So, even if the assumption made by the company that the efficacy associated with bilateral and unilateral transplants is the same and all of the parameters employed by the company for resource use and utility reflect reality, the 3.5% pa discount rate should be applied as patients are not restored to 'close to full health'. The ICERs for Holoclar would then be at or exceed £30,000 per QALY gained when Holoclar is compared to Lr-CLAL and KLAL for patients with bilateral LSCD treated in both eyes.

The reason for the marked increase in the size of the ICERs per QALY gained is largely due to the decrease in the incremental QALY benefits from Holoclar. With a higher discount rate, the QALY benefits from Holoclar are now more heavily discounted than they were previously. In addition, as the majority of the costs of Holoclar are up front (mostly incurred in the first year and therefore are largely undiscounted), the costs of BSC and failed transplant exist in the future; this means that a higher discount rate reduces the costs of BSC and failed transplant more than it reduces the costs of Holoclar.

### 5.4.4 Use of autologous serum eye drops

The ERG has reviewed the cost and resource use assumptions and values used in the company's economic models. Clinical expert advice to the ERG is that there are a number of aspects related to cost and resource use in the company models that would not be relevant to the use of Holoclar (or the other procedures) in the NHS. For example, the ERG's clinical experts do not accept the company's assumptions about the use of bandage contact lenses

and the need for ophthalmic outpatient appointments. However, any changes to these parameters only influence the size of the ICER per QALY gained by less than 1% and so are considered to be minor and are not included in the ERG's amendments table.

More importantly, a difference in opinion between clinical experts exists for the use of autologous serum eye drops. In two key areas the changes recommended by the ERG have a significant impact on the size of the estimated incremental costs between procedures.

**The use of autologous serum eye drops post-operatively**

In the company model it is assumed that patients use autologous serum eye drops for a 3-month period after all procedures except for Holoclar. It was stated in the CS (p32) and in response to a clarification question from the ERG (REF CQ B5) that this was because, in the SmPC[30] and clinical study reports of Holoclar,[41-43,50] autologous serum eye drops were not reported to be used post-operatively. Clinical advice to the company was that these eye drops are however used post-operatively for CLAU, Lr-CLAL and KLAL.

There are no clinical guidelines on the post-operative use of autologous serum eye drops and all of the transplant procedures into the recipient eye are essentially identical. The ERG therefore considers it unlikely that a surgeon currently using autologous serum eye drops with CLAU, Lr-CLAL or KLAL will not use autologous serum eye drops should they start to treat patients using Holoclar. Conversely, if a surgeon is not currently using autologous serum eye drops with CLAU, Lr-CLAL or KLAL, they would not then use them for Holoclar. In either case, the ERG considers that autologous serum eye drops should be used for all procedures or for none of the procedures considered in the company model. Adding or removing a cost that is the same for all procedures makes no difference to the size of the incremental costs estimated between procedures; adding the cost of post-operative autologous serum eye drops to Holoclar or removing the cost from the alternative procedures has equal effect on the size of the ICER per QALY gained. The ERG has therefore added the cost to Holoclar.

In the unilateral case, when comparing Holoclar versus Lr-CLAL, using serum eye drops for all procedures post-operatively increases the incremental costs from £[redacted] to £[redacted] with the ICER increasing to £8,129 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £3,239 per QALY gained. Holoclar continues to dominate BSC. Holoclar remains dominated by CLAU although the incremental costs increase from £[redacted] to £[redacted].

In the bilateral case, for the comparison of Holoclar versus Lr-CLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £13,923 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted]

[redacted] with the ICER increasing to £8,130 per QALY gained. Versus BSC, Holoclar is no longer cost saving and there are additional costs of £[redacted] with an ICER of £351 per QALY gained. There is no comparison of Holoclar versus CLAU.

**The use of autologous serum eye drops for flare-up**

In the company model it is assumed that two flare-ups per year occur for patients with LSCD either on BSC or after transplant failure. During each flare-up the patient is provided with autologous serum eye drops. In the company base case, autologous serum eye drops for flare-up account for £[redacted] (88.0%) of the cost of BSC, £[redacted] (76.5%) of the cost of Lr-CLAL and £[redacted] (61.0%) of the cost of KLAL but account for only £[redacted] (21.7%) of the cost of Holoclar. The actual number of flare-ups and the frequency of use of autologous serum eye drops are by far the biggest drivers of costs in the company model for Lr-CLAL, KLAL and BSC.

The company has based the use of autologous serum eye drops on the advice of clinicians who were presented with a list of products (including autologous serum eye drops) that could be used to treat flare-ups. The responses from the clinicians were that all of the products could be used at some stage, with one clinician estimating the cost of BSC to be £[redacted] per year. However, the ERG sought clinical advice on the use of autologous serum eye drops for flare-up and was informed that they were not routinely used in the NHS. Part of the problem with this treatment is that it can take 4 weeks to manufacture autologous serum eye drops (http://hospital.blood.co.uk/media/2136/84065ff9-6ce6-422e-99ed-b9dd86393cb6.pdf) and if flare-ups happen they may resolve before the eye drops are manufactured. Again, it seems that clinical practice varies by surgeon.

The ERG is of the opinion that, due to the lack of clarity on the use of autologous serum eye drops when used to treat patients with flare-ups, two scenarios (i.e., treatment with and without the use of autologous serum drops for flare-ups) must be considered.

The company base case model includes the use of serum autologous eye drops.

An ERG amendment therefore considers the impact on the size of the ICER per QALY gained when autologous serum eye drops are **not** used to treat flare-ups in the unilateral case. When comparing Holoclar with Lr-CLAL, the incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £23,328 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £16,766 per QALY gained. Versus BSC, Holoclar is no longer cost saving and there are now additional costs of £[redacted] with an ICER of £12,467 per QALY gained. Holoclar remains dominated by CLAU, although the incremental costs decrease from £[redacted] to £[redacted].

In the bilateral case, incremental costs increase from £[redacted] to £[redacted] versus Lr-CLAL with the ICER increasing to £37,138 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £28,237 per QALY gained. Versus BSC, Holoclar is no longer cost saving and there is now an additional cost of £[redacted] with an ICER of £18,980 per QALY gained. There is no comparison of Holoclar versus CLAU.

### 5.4.5 Use of KLAL after failure with Lr-CLAL

The company has assumed that patients are only eligible for one type of procedure for their LSCD. In practice, the ERG considers it is not unlikely that a second living relative donation for Lr-CLAL may be available from the living relative who provided the first donation as cells can also be taken from the other eye. Indeed, this is the implicit assumption that permits the use of Lr-CLAL to treat both eyes of a patient with bilateral LSCD. It is also unlikely that whilst patients can have up to three KLAL transplants they will not be eligible for KLAL should Lr-CLAL fail.

The ERG therefore considers that a more plausible scenario is to allow patients with unilateral LSCD to undergo at least two attempts with Lr-CLAL; this can be interpreted as two genuine attempts at Lr-CLAL or as a proxy for one attempt with Lr-CLAL and one attempt with KLAL as the costs and effectiveness of both treatments are broadly comparable.

For bilateral patients, the ERG has assumed that only one attempt will be made with Lr-CLAL. If only one relative comes forward to donate cells then donations from both eyes are required to treat the two damaged eyes of the patient and so therefore the relative would not be able to donate again should either transplant fail. However, it is possible that the patient could be eligible for KLAL; this is another reason that the bilateral results need to be treated with caution.

Allowing Lr-CLAL to be used twice increases both the incremental cost of Holoclar over Lr-CLAL (from £[redacted] to £[redacted]) whilst reducing the QALY gain from 2.36 to 1.12. This has the effect of increasing the size of the ICER to £30,415 per QALY gained.

# 6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

This section summarises the impact of the ERG's amendments to the company's models when Holoclar is compared to CLAU, Lr-CLAL, KLAL and BSC in patients with unilateral moderate to severe LSCD and when Holoclar is compared to Lr-CLAL, KLAL and BSC in patients with bilateral moderate to severe LSCD.

The ERG has only considered the changes in the model that would have a major impact on the size of the ICERs and has not considered the minor issues described in Section 5 (e.g., the slight implausibility of the pain decrement and the difference in clinical opinion on frequency of outpatient appointments).

## *6.1 Unilateral LSCD (Table 33 to Table 36)*

For patients with unilateral LSCD, whilst most of the amendments made by the ERG reduce the cost and QALY differential when Holoclar is compared to CLAU, in all cases CLAU remains the dominant strategy generating more QALYs than Holoclar at a lower cost.

For Lr-CLAL and KLAL the ERG amendments increase the ICER to £152,590 per QALY gained and £33,473 per QALY gained respectively if autologous serum eye drops continue to be used for flare-ups. If autologous serum eye drops are not used routinely for flare-ups as suggested by clinical advice to the ERG, then the ICERs increase further to £179,066 per QALY gained for Holoclar compared to Lr-CLAL and to £60,996 for Holoclar compared to Lr-CLAL. Even if Lr-CLAL is only used once in practice, with no opportunity for a second procedure on failure be it Lr-CLAL or KLAL, then the ICER would still increase to £45,048 per QALY gained if autologous serum eye drops were routinely used for flare-ups and £76,963 per QALY gained if they were not routinely used for flare-ups.

Compared to BSC, the ERG amendments show Holoclar continues to dominate or have an ICER no higher than £12,500 per QALY gained unless all of the ERG amendments were taken into account with autologous serum eye drops **not** being routinely used for flare-ups. In this case, the ICER for Holoclar compared to BSC is £35,489 per QALY gained.

## *6.2 Bilateral LSCD (Table 37 to Table 39)*

For patients with bilateral LSCD, when Holoclar is compared to Lr-CLAL, simply applying a 3.5% pa discount rate to costs and benefits increases the ICER to £34,817 per QALY gained. If all of the ERG amendments are implemented then the ICER increases to £67,219 per QALY gained if autologous serum eye drops are routinely used for flare-ups and to £111,654 per QALY gained if they are not. These ICERs are based on the assumption that patients with bilateral LSCD would not be eligible for KLAL if Lr-CLAL failed.

When Holoclar is compared to KLAL, applying the 3.5% pa discount rate to costs and benefits increases the ICER to £29,818 per QALY gained. If all the ERG amendments are implemented then the ICER increases to £75,457 per QALY gained if autologous serum eye drops are routinely used for flare-ups and to £122,468 per QALY gained if they are not.

When Holoclar is compared with BSC, the ERG amendments show that Holoclar continues to dominate or has an ICER no higher than £19,000 per QALY gained unless all of the ERG amendments are implemented with autologous serum eye drops **not** being routinely used for flare-ups. In this case, the ICER for Holoclar compared to BSC is £50,973 per QALY gained.

There is no comparison of Holoclar versus CLAU.

Table 33 ERG adjustments to company base case: Holoclar versus CLAU (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | CLAU | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | **£[redacted]** | ***12.09*** | ***£22,158*** | ***12.64*** | [redacted] | ***-0.55*** | ***Dominated*** | |
| R1) Use of Brown 2003 VA utility values | £[redacted] | 16.43 | £22,158 | 16.95 | [redacted] | -0.52 | Dominated | - |
| R2) ERG preferred decrement for disfigurement | £[redacted] | 15.11 | £22,158 | 15.41 | [redacted] | -0.31 | Dominated | |
| **B. ERG preferred utility scenario (R1+R2)** | **£[redacted]** | **19.44** | **£22,158** | **19.72** | [redacted] | **-0.28** | **Dominated** | |
| R3) 3.5% discount rate | £[redacted] | 8.93 | £18,651 | 9.34 | [redacted] | -0.41 | Dominated | |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | **£[redacted]** | **14.40** | **£18,651** | **14.60** | [redacted] | **-0.21** | **Dominated** | |
| R4) Autologous serum eye drops post-operatively with Holoclar | £[redacted] | 12.09 | £22,158 | 12.64 | [redacted] | -0.55 | Dominated | |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | **£[redacted]** | **14.40** | **£18,651** | **14.60** | [redacted] | **-0.21** | **Dominated** | |
| R5) Autologous serum eye drops not used in flare-ups | £[redacted] | 12.09 | £10,358 | 12.64 | [redacted] | -0.55 | Dominated | |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of autologous serum eye drops for flare-ups (R1-R5)** | **£[redacted]** | **14.40** | **£9,901** | **14.60** | [redacted] | **-0.21** | **Dominated** | |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; CLAU=conjunctival limbal autograft

Table 34 ERG adjustments to company base case: Holoclar versus Lr-CLAL (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | Lr-CLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***12.09*** | ***£77,434*** | ***9.73*** | [redacted] | ***2.36*** | ***£7,185*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 16.43 | £77,434 | 14.18 | [redacted] | 2.24 | £7,576 | £391 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 15.11 | £77,434 | 13.79 | [redacted] | 1.31 | £12,960 | £5,775 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **19.44** | **£77,434** | **18.25** | [redacted] | **1.19** | **£14,291** | **£7,106** |
| R3) 3.5% discount rate | [redacted] | 8.94 | £55,782 | 7.41 | [redacted] | 1.53 | £21,182 | £13,998 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **14.40** | **£55,782** | **13.63** | [redacted] | **0.77** | **£42,139** | **£34,954** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 12.09 | £77,434 | 9.73 | [redacted] | 2.36 | £8,129 | £945 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **14.40** | **£55,782** | **13.63** | [redacted] | **0.77** | **£45,048** | **£37,863** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 12.09 | £18,222 | 9.73 | [redacted] | 2.36 | £23,328 | £16,143 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **14.40** | **£15,587** | **13.63** | [redacted] | **0.77** | **£76,963** | **£69,778** |
| R6) Two attempts at Lr-CLAL | [redacted] | 12.10 | £60,373 | 10.97 | [redacted] | 1.12 | £30,415 | £23,230 |
| **F. All suggested changes from ERG but continued use of autologous serum eye drops for flare-up (R1-R4, R6)** | [redacted] | **14.40** | **£43,805** | **14.09** | [redacted] | **0.31** | **£152,590** | **£145,405** |
| **G. All suggested changes from ERG (R1-R6)** | [redacted] | **14.40** | **£20,038** | **14.09** | [redacted] | **0.31** | **£179,066** | **£171,881** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; Lr-CLAL=conjunctival limbal allograft from a live related donor

Table 35 ERG adjustments to company base case: Holoclar versus KLAL (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | KLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***12.09*** | ***£89,256*** | ***9.80*** | [redacted] | ***2.29*** | ***£2,255*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 16.43 | £89,256 | 14.24 | [redacted] | 2.18 | £2,367 | £112 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 15.11 | £89,256 | 13.85 | [redacted] | 1.26 | £4,107 | £1,852 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **19.44** | **£89,256** | **18.29** | [redacted] | **1.15** | **£4,494** | **£2,240** |
| R3) 3.5% discount rate | [redacted] | 8.93 | £65,932 | 7.48 | [redacted] | 1.46 | £15,245 | £12,990 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **14.40** | **£65,932** | **13.67** | [redacted] | **0.73** | **£30,415** | **£28,160** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 12.09 | £89,256 | 9.80 | [redacted] | 2.29 | £3,239 | £975 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **14.40** | **£65,932** | **13.67** | [redacted] | **0.73** | **£33,473** | **£31,219** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 12.09 | £34,960 | 9.80 | [redacted] | 2.29 | £16,766 | £14,512 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **14.40** | **£30,147** | **13.67** | [redacted] | **0.73** | **£60,996** | **£58,741** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; KLAL=keratolimbal allograft

Table 36 ERG adjustments to company base case: Holoclar versus BSC (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | BSC | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***12.09*** | ***£101,535*** | ***7.18*** | [redacted] | ***4.91*** | ***Dominates*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 16.43 | £101,535 | 12.10 | [redacted] | 4.33 | Dominates | - |
| R2) ERG preferred decrement for disfigurement | [redacted] | 15.11 | £101,535 | 12.01 | [redacted] | 3.10 | Dominates | - |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **19.44** | **£101,535** | **16.92** | [redacted] | **2.52** | **Dominates** | **-** |
| R3) 3.5% discount rate | [redacted] | 8.93 | £75,289 | 5.33 | [redacted] | 3.61 | £3,563 | - |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **14.40** | **£75,289** | **12.55** | [redacted] | **1.85** | **£6,948** | **-** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 12.09 | £101,535 | 7.18 | [redacted] | 4.91 | Dominates | - |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **14.40** | **£75,289** | **12.55** | [redacted] | **1.85** | **£8,155** | **-** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 12.09 | £12,188 | 7.18 | [redacted] | 4.91 | £12,467 | - |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **14.40** | **£9,037** | **12.55** | [redacted] | **1.85** | **£35,489** | **-** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; BSC=best supportive care, ERG=Evidence Review Group; BSC=best supportive care

Table 37 ERG adjustments to company base case: Holoclar versus Lr-CLAL (bilateral model)

| *Scenario/ERG amendment* | Holoclar | | Lr-CLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***9.25*** | ***£155,430*** | ***6.36*** | [redacted] | ***2.89*** | ***£12,438*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 13.05 | £155,430 | 10.47 | [redacted] | 2.59 | £13,916 | £1,478 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 12.34 | £155,430 | 10.43 | [redacted] | 1.90 | £18,890 | £6,452 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **16.14** | **£155,430** | **14.54** | [redacted] | **1.60** | **£22,524** | **£10,086** |
| R3) 3.5% discount rate | [redacted] | 6.77 | £112,364 | 4.93 | [redacted] | 1.85 | £34,817 | £22,379 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **11.93** | **£112,364** | **10.91** | [redacted] | **1.02** | **£63,047** | **£50,609** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 9.25 | £155,430 | 6.36 | [redacted] | 2.89 | £13,923 | £1,485 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **11.93** | **£112,364** | **10.91** | [redacted] | **1.02** | **£67,219** | **£54,781** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 9.25 | £36,358 | 6.36 | [redacted] | 2.89 | £37,138 | £24,700 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **11.93** | **£30,948** | **10.91** | [redacted] | **1.02** | **£111,654** | **£99,216** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; Lr-CLAL=conjunctival limbal allograft from a live related donor

Table 38 ERG adjustments to company base case: Holoclar versus KLAL (bilateral model)

| *Scenario/ERG amendment* | Holoclar | | KLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***9.25*** | ***£173,844*** | ***6.56*** | [redacted] | ***2.69*** | ***£6,533*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 13.05 | £173,844 | 10.71 | [redacted] | 2.34 | £7,512 | £979 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 12.34 | £173,844 | 10.70 | [redacted] | 1.63 | £10,762 | £4,229 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **16.14** | **£173,844** | **14.86** | [redacted] | **1.28** | **£13,702** | **£7,169** |
| R3) 3.5% discount rate | [redacted] | 6.77 | £127,407 | 5.12 | [redacted] | 1.65 | £29,818 | £23,285 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **11.93** | **£127,407** | **11.22** | [redacted] | **0.71** | **£69,455** | **£62,922** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 9.25 | £173,844 | 6.56 | [redacted] | 2.69 | £8,130 | £1,597 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **11.93** | **£127,407** | **11.22** | [redacted] | **0.71** | **£75,457** | **£68,924** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 9.25 | £67,855 | 6.56 | [redacted] | 2.69 | £28,237 | £21,704 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **11.93** | **£57,970** | **11.22** | [redacted] | **0.71** | **£122,468** | **£115,935** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; KLAL= keratolimbal allograft

Table 39 ERG adjustments to company base case: Holoclar versus BSC (bilateral model)

| *Scenario/ERG amendment* | Holoclar | | BSC | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| **A. Company's base case** | [redacted] | **9.25** | **£193,323** | **2.44** | [redacted] | **6.81** | **Dominates** | - |
| R1) Use of Brown 2003 VA utility values | [redacted] | 13.05 | £193,323 | 7.72 | [redacted] | 5.33 | Dominates | - |
| R2) ERG preferred decrement for disfigurement | [redacted] | 12.34 | £193,323 | 7.26 | [redacted] | 5.07 | Dominates | - |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **16.14** | **£193,323** | **12.54** | [redacted] | **3.60** | **Dominates** | - |
| R3) 3.5% discount rate | [redacted] | 6.77 | £143,350 | 1.81 | [redacted] | 4.96 | £6,708 | - |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **11.93** | **£143,350** | **9.30** | [redacted] | **2.63** | **£12,669** | - |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 9.25 | £193,323 | 2.44 | [redacted] | 6.81 | £351 | - |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **11.93** | **£143,350** | **9.30** | [redacted] | **2.63** | **£14,288** | - |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 9.25 | £14,629 | 2.44 | [redacted] | 6.81 | £18,980 | - |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **11.93** | **£10,847** | **9.30** | [redacted] | **2.63** | **£50,973** | - |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; BSC=best supportive care

## 6.3 Conclusions of the ERG's cost effectiveness review

The ERG considers that there are several fundamental issues that cast doubt on the cost effectiveness of Holoclar versus all comparators.

First, the results of the company's base case unilateral model demonstrate that Holoclar is more expensive and less effective than CLAU. All, except one, of the amendments recommended by the ERG decrease the costs and benefits associated with Holoclar, reduce the incremental costs and increase the incremental benefits estimated when comparing Holoclar versus CLAU. Even if CLAU and Holoclar were to have the same rate of transplant success CLAU would still dominate Holoclar; CLAU is a significantly less costly procedure than Holoclar. If CLAU is currently used to treat patients with unilateral LSCD in the NHS, then the cost effectiveness evidence presented by the company suggests that failing to use CLAU in favour of any of the alternatives, including Holoclar, would generate worse patient outcomes at a higher cost.

Second, the clinical effectiveness evidence base for all of the procedures is weak as most of the data available are derived from case series studies. Case series studies by design yield low quality evidence even if well conducted. The effectiveness data for the comparators is drawn from a pooling of data from case series studies; in the CS the company claimed that pooling would be inappropriate due to parameter heterogeneity. The ERG agrees that it is inappropriate to pool these data but considers that use of the pooled data in the model generates no less robust results than the arbitrary selection of data from one of the small case series studies. However, the weakness of the underlying data – pooled or otherwise - casts significant doubt on the robustness of the ICERs per QALY gained built upon these data.

Third, the clinical effectiveness evidence provided by the company to support the use of Holoclar to treat both eyes in patients with bilateral LSCD is limited to data describing one patient. Given there are plausible clinical reasons as to why Holoclar may not be as effective when used to treat bilateral LSCD compared with use in unilateral LSCD, the ERG considers that the cost effectiveness results from the bilateral model are of extremely limited value to the point of being non-informative.

Fourth, the ERG considers that the utility values incorporated into the company models were implausibly low and the disutility value used for disfigurement was implausibly high. The ERG therefore used more plausible utility values in the model and these changes had substantial impacts on the size of the ICERs per QALY gained.

Fifth, the discount rate applied by the company should be 3.5% pa rather than 1.5% pa. NICE only permits the use of a lower discount rate if an intervention cures terminal illness or removes a significant detriment to HRQoL such that a patient lives at or near full health for the remainder

of their life. The ERG considers that neither of these clauses applies to treatment with Holoclar. In the bilateral model, simply applying the 3.5% pa discount rate increases the size of the ICER per QALY gained; the ICER for Holoclar versus Lr-CLAL is £34,849 per QALY gained and the ICER for Holoclar versus KLAL is £29,852 per QALY gained.

Sixth, there is some doubt about where the use of autologous serum eye drops sits in the treatment pathway, especially when used to treat patients with flare-ups. As the cost of using these eye drops to treat flare-ups accounts for the majority of the cost of BSC – which patients with failed transplants move onto – accurate costing of their use significantly affects the size of the ICER per QALY gained.

Seventh, the ERG considers it implausible that patients with unilateral LSCD who fail after Lr-CLAU are not offered a second procedure.

Finally, the models were not designed to include failure rates beyond 12 months after a successful transplant. This is an issue for the evaluation of CLAU where clinical advice provided to the company suggested that failure rates at 10 years could be as high as 30%. This in turn becomes an issue for Holoclar where real world transplant success rates at 10 years are essentially non-existent; if stable transplants for CLAU can fail many years after successful transplant this could also be the case for Holoclar. If CLAU and Holoclar can fail post 12 months after transplant, then the models will systematically underestimate the true ICERs per QALY gained for CLAU and Holoclar compared to the alternative treatments.

In the unilateral LSCD model, application of the ERG changes to utility values, discount rates and modifications to the use of autologous serum eye drops resulted in ICERs for Holoclar remaining dominated by CLAU with an incremental cost of £[redacted] (R1-R5). Versus Lr-CLAL, the ICER is £179,066 per QALY gained (this ICER includes a second procedure after initial transplant failure, R1-R6). Versus KLAL, the ICER is £60,996 per QALY gained (R1-R5). Compared to BSC, the ICER is £35,489 per QALY gained (R1-R5).

In the bilateral LSCD model, application of the ERG changes to utility values, discount rates and modifications to the use of autologous serum eye drops resulted in ICERs for Holoclar versus Lr-CLAL of £116,654 per QALY gained (R1-R5). Versus KLAL, the ICER is £122,468 per QALY gained (R1-R5). Versus BSC, the ICER is £50,973 per QALY gained (R1-R5).

# 7 END OF LIFE

The company has not put forward a case for Holoclar to be considered under the NICE End of Life criteria. The ERG agrees that this is appropriate.

# 8 DISCUSSION

The primary source of clinical effectiveness evidence for Holoclar provided by the company is derived from a single, retrospective case series study (the HLSTM01 study) of 104 patients with LSCD due to ocular burns. LSCD due to ocular burns is a rare condition and so a study of 104 patients is a sizeable study; however, a case series study (particularly when conducted retrospectively) has an inherently weak study design and the results are descriptive rather than analytical. In the absence of an appropriate comparator arm in the HLSTM01 case series study, it is difficult to evaluate the true clinical effectiveness of Holoclar. The company was unable to identify any reliable evidence for the clinical effectiveness of any of the stated comparators to Holoclar. As a result, it was inappropriate to carry out an ITC and the evidence for the clinical effectiveness of treatment with Holoclar versus all comparators is largely reliant on the results of retrospective case series studies.

A further difficulty in the evaluation of the outcomes of the HLSTM01 study is that no HRQoL data were collected. This means that the HRQOL impact of treatment with Holoclar treatment is unknown.

The company makes the claim that Holoclar can be used to treat both eyes in patients with moderate to severe LSCD and, further, assumes that treatment of the second eye is as effective as treatment of the first eye. However, the company has not provided any clinical evidence to support either the claim or the ensuing assumption.

The treatment of LSCD due to ocular burns is a highly specialised area for which there are no agreed treatment protocols, no standard comparator treatments and no licensed treatments, other than Holoclar, are available. Lack of consensus in these areas poses problems when evaluating the cost effectiveness of Holoclar. A particular issue for this appraisal is variation in the use (or otherwise) of autologous serum eye drops as, depending on how they are used, the cost of the eye drops has a substantial impact on the size of the ICERs per QALY gained.

The company has initiated three further studies[50,95,96] of Holoclar (HOLOCORE, HOLOCORE-FU AND HOLOSIGHT) and, whilst all are multinational prospective studies, all are designed as observational studies and do not include control groups. The company discusses (CS, p72) the difficulties inherent in designing a RCT to evaluate the clinical effectiveness of Holoclar. The barriers to designing and conducting such a RCT are numerous and include ethical and practical considerations. Although the ERG agrees that a RCT of the technology would be

challenging, the ERG notes that a small RCT[49] has already been carried out in this area. The ERG cautions that studies of similar technologies to Holoclar are likely to emerge and a rigorous, standardised approach to the design and analysis of these clinical studies is needed

# 9 OVERALL CONCLUSIONS

## *9.1 Implications for research*

As there are no HRQoL data relevant to the use of Holoclar or any of the comparator treatments, studies providing HRQoL data would be welcomed. The company plans to collect HRQoL data relevant to Holoclar data from the patients recruited to the HOLOCORE,[50] HOLOCORE-FU[95,96] and the HOLOSIGHT[95] studies. The results of the first of the studies (HOLOCORE[50]) are likely to be available in 2020.

There is a lack of evidence to support the clinical effectiveness of treatment with Holoclar in patients with bilateral LSCD due to ocular burns who have both eyes treated. Future studies should collect data pertinent to treatment outcomes for these patients. The data collected should enable a comparison of treatment outcomes between the first and second treated eyes.

Further evidence of the duration of treatment beyond 1 year is also needed. The three studies[50,95,96] planned by the company are intended to collect data for up to 5 years post-transplantation.

# 10 REFERENCES


1. Chiesi Ltd. Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]: Company evidence submission to NICE 2016.
2. Dua HS, Joseph A, Shanmuganathan VA, Jones RE. Stem cell differentiation and the effects of deficiency. Eye. 2003; 17:877-85.
3. Shaharuddin B, Ahmad S, Ali S, Meeson A. Limbal side population cells: A future treatment for limbal stem cell deficiency. Regen Med. 2013; 8:319-31.
4. Sejpal K, Bakhtiari P, Deng SX. Presentation, diagnosis and management of limbal stem cell deficiency. Middle East Afr J Ophthalmol. 2013; 20:5-10.
5. Dua HS, Miri A, Said DG. Contemporary limbal stem cell transplantation - a review. Clin Experiment Ophthalmol. 2010; 38:104-17.
6. Haagdorens M, Van Acker SI, Van Gerwen V, Ni Dhubhghaill S, Koppen C, Tassignon MJ*, et al.* Limbal stem cell deficiency: Current treatment options and emerging therapies. Stem Cells Int. 2016; 2016:9798374.
7. Hatch K, Dana R. The structure and function of the limbal stem cell and the disease states associated with limbal stem cell deficiency. Int Ophthalmol Clin. 2009; 149:43-52.
8. Osei-Bempong C, Figueiredo FC, Lako M. The limbal epithelium of the eye-a review of limbal stem cell biology, disease and treatment. BioEssays : news and reviews in molecular, cellular and developmental biology. 2013; 35:211-9.
9. Espana EM, Grueterich M, Romano AC, Touhami A, Tseng SC. Idiopathic limbal stem cell deficiency. Ophthalmology. 2002; 109:2004-10.
10. Lichtinger A, Pe'er J, Frucht-Pery J, Solomon A. Limbal stem cell deficiency after topical mitomycin C therapy for primary acquired melanosis with atypia. Ophthalmology. 2010; 117:431-7.
11. Burcu A, Yalniz-Akkaya Z, Ozdemir MF, Erdem E, Onat MM, Ornek F. Surgical rehabilitation following ocular chemical injury. Cutan Ocul Toxicol. 2014; 33:42-8.
12. Crawford AZ, McGhee CN. Management of limbal stem cell deficiency in severe ocular chemical burns. Clin Experiment Ophthalmol. 2012; 40:227-9.
13. European Medicines Agency. Assessment Report: Holoclar 2014.
14. Macdonald EC, Cauchi PA, Azuara-Blanco A, Foot B. Surveillance of severe chemical corneal injuries in the UK. Br J Ophthalmol. 2009; 93:1177-80.
15. Baylis O, Figueiredo F, Henein C, Lako M, Ahmad S. 13 years of cultured limbal epithelial cell therapy: a review of the outcomes. J Cell Biochem. 2011; 112:993-1002.
16. Bobba S, Chow S, Watson S, Di Girolamo N. Clinical outcomes of xeno-free expansion and transplantation of autologous ocular surface epithelial stem cells via contact lens delivery: a prospective case series. Stem Cell Res Ther. 2015; 6:23.
17. Graham JS, Schoneboom BA. Historical perspective on effects and treatment of sulfur mustard injuries. Chem Biol Interact. 2013; 206:512-22.
18. Shortt AJ, Tuft SJ, Daniels JT. Corneal stem cells in the eye clinic. Br Med Bull. 2011; 100:209-25.
19. Medical Advisory Secretariat. Limbal stem cell transplantation: An evidence-based analysis. Ontario Health Technology Assessment Series. 2008; 8.
20. World Health Organisation. Socio economic aspects of blindness and visual impairment. 2016; Available from: http://www.who.int/blindness/economy/en/ [accessed September 2016].
21. Chiesi Farmaceutici S.p.A. Notes from meeting with Mr Alex Shortt 22nd June 2016 (CHHOL20160794). Data on file. 2016.
22. Ramachandran C, Basu S, Sangwan VS, Balasubramanian D. Concise review: the coming of age of stem cell treatment for corneal surface damage. Stem Cells Transl Med. 2014; 3:1160-8.

23. Rao SK, Rajagopal R, Sitalakshmi G, Padmanabhan P, Rao SK, Rajagopal R, *et al.* Limbal autografting: comparison of results in the acute and chronic phases of ocular surface burns. Cornea. 1999; 18:164-71.
24. Dua S, Azuara-Blanco A. Allo-limbal transplantation in patients with limbal stem cell deficiency. Br J Ophthalmol. 1999; 83:414-9.
25. Cauchi PA, Ang GS, Azuara-Blanco A, Burr JM. A systematic literature review of surgical interventions for limbal stem cell deficiency in humans. Am J Ophthalmol. 2008; 146:251-9.
26. Miri A, Al-Deiri B, Dua HS. Long-term outcomes of autolimbal and allolimbal transplants. Ophthalmology. 2010; 117:1207-13.
27. Gomes JA, dos Santos MS, Cunha MC, Mascaro VL, Nadai Barros J, de Sousa LB. Amniotic membrane transplantation for partial and total limbal stem cell deficiency secondary to chemical burn. Ophthalmology. 2003; 110:466-73.
28. Fish R, Davidson RS. Management of ocular thermal and chemical injuries, including amniotic membrane therapy. Current Opinion in Ophthalmology. 2010; 21:317-1.
29. Ucakhan OO, Koklu G, Firat E. Nonpreserved human amniotic membrane transplantation in acute and chronic chemical eye injuries. Cornea. 2002; 21:169-72.
30. Chiesi Farmaceutici S.p.A. Summary of Product Characteristics. Holoclar.2015.
31. National Institute for Health and Care Excellence. IPG216: Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium. Interventional procedure guidance. 2007; Available from: nice.org.uk/guidance/ipg216 [accessed 31st August 2016].
32. National Institute for Health and Care Excellence. NICE Pathways: Eye conditions overview London: NICE; 2015; Available from: http://pathways.nice.org.uk/pathways/eye-conditions [accessed August 2016].
33. Department of Health. The NHS Outcomes Framework 2015/16.2014.
34. NHS England. Manual for prescribed specialised services 2013/14. 2016.
35. NHS England. NHS Standard contract for specialised ophthalmology (adult). 2016.
36. NHS England. 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness.2013.
37. European Medicines Agency. History of the EMA. 2016; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp&mid=WC0b01ac058087addd [accessed Sept 2016].
38. Office for National Statistics. Annual Mid-year Population Estimates, 2014. 2015.
39. Medi-Pragma. Limbal Stem Cell Deficiency Market Potential Analysis Summary Report. 2012. Data on file.2012.
40. National Institute for Health and Care Excellence. Final scope: Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns ID899 2016.
41. Chiesi Farmaceutici S.p.A. HLSTM01 Clinical Study Report 2012.
42. Chiesi Farmaceutici S.p.A. HLSTM02 Clinical Study Report 2012.
43. Chiesi Farmaceutici S.p.A. HLSTM04 Clinical Study Report 2014.
44. Marchini G, Pedrotti E, Pedrotti M, Barbaro V, Di Iorio E, Ferrari S, *et al.* Long-term effectiveness of autologous cultured limbal stem cell grafts in patients with limbal stem cell deficiency due to chemical burns. Clinical & Experimental Ophthalmology. 2012; 40:255-67.
45. Pellegrini G, Rama P, Matuska S, Lambiase A, Bonini S, Pocobelli A, *et al.* Biological parameters determining the clinical outcome of autologous cultures of limbal stem cells. Regen Med. 2013; 8:553-67.
46. Pellegrini G, Traverso CE, Franzi AT, Zingirian M, Cancedda R, De Luca M. Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. The Lancet. 1997; 349:990-3.
47. Rama P, Bonini S, Lambiase A, Golisano O, Paterna P, De Luca M, *et al.* Autologous fibrin-cultured limbal stem cells permanently restore the corneal surface of patients with total limbal stem cell deficiency. Transplantation. 2001; 72:1478-85.

48. Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, G. P. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010; 363:147-55.
49. Titiyal JS, Sharma N, Agarwal AK, Prakash G, Tandon R, Vajpayee R. Live related versus cadaveric limbal allograft in limbal stem cell deficiency. Ocul Immunol Inflamm. 2015; 23:232-9.
50. Chiesi Farmaceutici S.p.A. HOLOCORE: Clinical Study Protocol 2015.
51. Chiesi Farmaceutici S.p.A. Clinical Expert Opinion Questionnaire (CHHOL20160798). Data on file. 2016.
52. Basu S, Sureka SP, Shanbhag SS, Kethiri AR, Singh V, Sangwan VS. Simple limbal epithelial transplantation: Long-term clinical outcomes in 125 cases of unilateral chronic ocular surface burns. Ophthalmology. 2016; 123:1000-10.
53. Dickinson A, Lako M, Kolli S, Figueiredo FC. Outcomes of ex-vivo expanded limbal stem cell transplantation in humans. Cytotherapy. 2013; 15:S44-5.
54. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013; Available from: http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf (Accessed 01/06/2015).
55. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. 2015; Available from: https://www.nice.org.uk/article/pmg24/resources/non-guidance-single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf. [accessed April 2016].
56. The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual: 2016 edition. Australia: The Joanna Briggs Institute; 2016; Available from: http://joannabriggs.org/research/critical--appraisal--tools.html [accessed 31st August 2016].
57. Carey TS, Boden SD. A critical guide to case series reports. Spine (Phila Pa 1976). 2003:1631-4.
58. Kooistra B, Dijkman B, Einhorn TA, Bhandari M. How to design a good case series. The Journal of Bone and Joint Surgery. 2009; 91:Suppl 3 21-6.
59. Anderson DF. Amniotic membrane transplantation for partial limbal stem cell deficiency. Br J Ophthalmol. 2001; 85:567-75.
60. Borderie V, Touzeau O, Bourcier T, Allouch C, Scheer S, Laroche L. Treatment of the sequelae of ocular burns using limbal transplantation. Journal Français d'Opthalmologie. 2003; 26:710-6.
61. Dua HS. The conjunctiva in corneal epithelial wound healing. Br J Ophthalmol. 1998; 82:1407-11.
62. Dua HS, Azuara-Blanco A. Autologous limbal transplantation in patients with unilateral corneal stem cell deficiency. Br J Ophthalmol. 2000; 84:273-8.
63. Eslani M, Baradaran-Rafii A, Movahedan A, Moss A, Holland E, Djalilian A. Late acute graft rejection after keratolimbal allograft. American Academy of Ophthalmology. 2015:PO051.
64. Fernandes M, Sangwan V, Rao S, Basti S, Sridhar M, Bansal A*, et al.* Limbal stem cell transplantation. Indian J Ophthalmol. 2004; 52:5-22.
65. Han ES, Wee WR, Lee JH, Kim MK. Long-term outcome and prognostic factor analysis for keratolimbal allografts. Graefes Arch Clin Exp Ophthalmol. 2011; 249:1697-704.
66. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. Trans Am Ophthalmol Soc. 1996; 94:677-743.
67. Huang T, Wang Y, Zhang H, Gao N, Hu A. Limbal allografting from living-related donors to treat partial limbal deficiency secondary to ocular chemical burns. Arch Ophthalmol. 2011; 129:1267-73.
68. Ilari L, Daya SM. Long-term outcomes of keratolimbal allograft for the treatment of severe ocular surface disorders. Ophthalmology. 2002; 109:1278-84.

69. Ivekovic R, Tedeschi-Reiner E, Novak-Laus K, Andrijevic-Derk B, Cima I, Mandic Z. Limbal graft and/or amniotic membrane transplantation in the treatment of ocular burns. Ophthalmologica. 2005; 219:297-302.
70. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. Ophthalmology. 1989; 96:709-22.
71. Kheirkhah A, Johnson DA, Paranjpe DR, Raju VK, Casas V, Tseng SC. Temporary sutureless amniotic membrane patch for acute alkaline burns. Arch Ophthalmol. 2008; 126:1059-66.
72. Maruyama-Hosoi F, Shimazaki J, Shimmura S, Tsubota K. Changes observed in keratolimbal allograft. Cornea. 2006; 25:377-82.
73. Meallet M, Espana E, Grueterich M, Ti S-E, Goto E, Tseng S. Amniotic membrane transplantation with conjunctival limbal autograft for total limbal stem cell deficiency. Ophthalmology. 2003; 110:1585-92.
74. Moldovan S, Borderie V, Baudrimont M, Laroche L. Treatment of unilateral limbal stem cell deficiency syndrome by limbal autograft. Journal Français Opthalmologie. 1999; 22:302-9.
75. Rauz S, Saw VP. Serum eye drops, amniotic membrane and limbal epithelial stem cells--tools in the treatment of ocular surface disease. Cell Tissue Bank. 2010; 11:13-27.
76. Schornack MM. Limbal stem cell disease: management with scleral lenses. Clin Exp Optom. 2011; 94:592-4.
77. Solomon A, Ellies P, Anderson DF, Touhami A, Grueterich M, Espana EM*, et al.* Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. Ophthalmology. 2002; 109:1159-66.
78. Tan DTH, Ficker LA, Buckley RJ. Limbal Transplantation. Ophthalmology. 1996; 103:29-36.
79. Torres J, Fernández I, Quadrado MJ, Murta J, Herreras J, Rodríguez-Ares MT*, et al.* Limbal transplantation: multicenter retrospective case series analysis. Arch Soc Esp Oftalmol. 2008; 83:417-22.
80. Tsai RJ, Tseng SC. Human allograft limbal transplantation for corneal surface reconstruction. Cornea. 2014; 13:389-400.
81. Tsubota K, Toda I, Saito H, Shinozaki N, Shimazaki J. Reconstruction of the corneal epithelium by limbal allograft transplantation for severe ocular surface disorders. Ophthalmology. 1995; 102:1486-96.
82. Fordham R, Ciminata G, Madoni A, Magni T, Ardigo D, Pelosi D*, et al.* Cost-effectiveness analysis of ex-vivo expanded autologous corneal epithelial cells containing stem cells to repair the damaged ocular surface in patients with moderate to severe limbal stem cell deficiency due to ocular burns in the UK. Value in Health. 2015; 18 (3):A298.
83. Department of Health. NHS Reference Costs 2014 to 2015. 2015; Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
84. Haymarket Media Group Ltd. MIMS Online2016.
85. Fielding S, Cummins E, Cruickshank M, Fraser C, Lois N, Brazzelli M. Aflibercept for treating diabetic macular oedema. 2014.
86. Beaudet A CJ, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modelling in type 2 diabetes. Value in Health. 2014; 17:462-70.
87. National Institute for Health and Care Excellence. Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension. 2009.
88. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value Health. 2009; 12:793-9.
89. Finger RP, Fenwick E, Hirneiss CW, Hsueh A, Guymer RH, Lamoureux EL*, et al.* Visual impairment as a function of visual acuity in both eyes and its impact on patient reported preferences. PLoS One. 2013; 8:e81042.

90. National Institute for Health and Care Excellence. TA409: Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion. 2016.
91. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Centre for Health Economics, University of York. 1999.
92. Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss. Ophthalmology. 2003; 110:1076-81.
93. Brown MM, Brown GC, Brown HC, Irwin B, Brown KS. The comparative effectiveness and cost-effectiveness of vitreoretinal interventions. Current Opinion in Ophthalmology. 2008; 19:202-17.
94. Brown G, Brown M, Brown H, Kindermann S, Sharma S. A Value-Based Medicine Comparison of Interventions for Subfoveal Neovascular Macular Degeneration. Ophthalmology. 2007; 114:1170-8.
95. Chiesi Farmaceutici S.p.A. HOLOSIGHT: Protocol outline. 2015.
96. Chiesi Ltd. HOLOCORE-FU: Clinical Study Protocol 2015.

# 11 APPENDICES

## Appendix 1 Summary of the Kooistra criteria for a good case series

The criteria for a good case series as suggested by Kooistra[58] includes specific guidelines for planning, conducting, and reporting a case series. The criteria has been split into three sections: design, analysis and reporting and a summary of the criteria under each heading is given below:

Design

-Study question is focused and includes the following information: (1) study population, (2) the intervention and (3) the primary outcome

-inclusion and exclusion criteria should be based on widely used, preferably validated definitions. If authors use their own criteria, definition and justification are necessary to enable the reader to compare the studied population with his or her own patients.

-case series includes consecutive inclusion of patients which reduces the chance of selection bias. Use of a short inclusion period minimizes known and unknown changes over time in co-interventions, prognosis and even in the intervention under study.

-detailed description of the intervention and co-intervention should be stated. It is very important to thoroughly describe co-interventions as these are not always standardized among study centres.

-outcomes measuring patient satisfaction, symptom-relief and a feeling of well-being should be included as clinical measurements alone would not represent the subjective nature of patient care.

-the blinding of outcome assessors should be implemented as this prevents the investigators measurements from being influenced by their personal treatment preference.

-the method of data acquisition should be addressed in the study report for the sake of repeatability and the appraisal of measurement bias.

-minimal length of follow-up should be provided so that sufficient time is given for complications to develop and be recorded.

Analysis

-only descriptive statistics should be used as the design of a case series is descriptive so no comparative tests yielding p-values should be done.

Reporting

-a statement of the external validity of the obtained data should be given which includes (1) patient characteristics and (2) completeness of follow-up.

-the presence of chance and the presence, direction, and magnitude of bias should be acknowledged.

-results of prognostic variables should be provided

-follow-up rates and reasons for loss to follow-up should be stated

-no absolute conclusions on the studied treatment should be stated

**Appendix 2** Details and outcomes of the HLSTM02 and HLSTM04 case series studies.

Kooistra[58] has proposed a criteria for evaluating the design, analysis and reporting of case series which have been applied to the HLSTM02 and HLSTM04 studies. Details of the criteria can be found in Appendix 1.

**HLSTM02.** The HLSTM02 case series study is small (n=29). The critique of HLSTM02 identified that the study question is not very detailed as the study population has not been described. Full inclusion and exclusion criteria are described in the protocol and the study authors state that the same surgical procedure was followed for all patients. However, the study authors do not highlight the timeline for when patients were enrolled into the study making it difficult for the ERG to assess whether selection bias is present and whether the length of inclusion period has affected the co-interventions, prognosis or even the intervention. The study also includes only efficacy and safety outcomes but no outcomes measuring patient satisfaction or mental well-being. Relevant subjective outcomes were assessed by an independent blinded assessor highlighting that the outcomes have not been influenced by the investigators in any way. The study authors only present descriptive statistics as suggested in the criteria and do not attempt to make absolute conclusions. Overall, the ERG is of the opinion that there are a number of flaws in the design of this case series such as study question not being detailed, the length of patient enrolment period has not been stated and lack of information about patient drop outs suggesting that HLSTM02 does not seem to be a good case series.

**HLSTM04**. The HLSTM04 case series study is small (n=15). The critique of HLSTM04 identified that the study question was sufficiently detailed but the study only included efficacy and safety outcomes without measuring patient satisfaction or mental well-being. The study includes a subjective primary and a secondary outcome on symptoms that have not been assessed by an independent blinded assessor raising concern over whether the outcomes may have been influenced by the investigators. The study authors only present descriptive statistics as suggested in the criteria. The study authors do not explain reasons for patients lost to follow-up but do mention there are high levels of missing data of 60% at baseline. Overall, from critiquing the HLSTM04 study the ERG is of the opinion that this is not a good case series as subjective outcomes have not been assessed by an independent blinded assessor so could have been influenced by the investigators and there are high levels of missing data present with no reasons provided on why they are missing.

## *11.1 Quality assessment of the HLSTM02 and HLSTM04 case series studies*

The company appraised the HLSTM01, the HLSTM02 and the HLSTM04 case series studies using the Joanna Briggs Institute (JBI)[56] checklist for case series studies. The JBI checklist includes 10 items, each of which is scored as *yes*, *no*, *unclear* or *not applicable*. The company states (CS, p118) that in its assessment, a *yes* response was marked as 1, whilst all the other possible responses were marked as zero. In this way, a maximum of 10 points could be awarded per study. The company reports that the two studies scored either a 9 or a 10; this suggests that the case series studies have a low risk of bias.

However, the ERG does not completely agree with the company's assessment (see Table 40). The ERG is unclear on how the company have assessed the criteria as sufficient information has not been provided in the protocols or the CSRs for the ERG to assess whether what the company are saying is valid or not. The company has not provided data on long-term follow-up The ERG did not have sufficient information to allow an assessment of one of the JBI criteria (whether the case series had consecutive inclusion of participants). The ERG considers that the company has not provided data on long-term follow-up and has not provided details on the length of inclusion of patients into the study. Therefore, the ERG is of the opinion that the case series studies may have a greater risk of bias than the company claims.

Table 40 Company's assessment of the risk of bias for the HLSTM02 and HLSTM04 case series studies with ERG comment

| JBI checklist criteria | HLSTM02 | HLSTM04 | ERG comment |
|---|---|---|---|
| Were there clear criteria for inclusion in the case series? | 1 | 1 | Agree |
| Was the condition measured in a standard, reliable way for all participants included in the case series? | 1 | 1 | Agree |
| Were valid methods used for identification of the condition for all participants included in the case series? | 1 | 1 | Agree |
| Did the case series have consecutive inclusion of participants? | 0 | 1 | The ERG is unclear how the company has assessed this criterion as sufficient information is not provided in the protocol or CSR to assess whether the case series studies have consecutively included participants or not. |
| Did the case series have complete inclusion of participants? | 1 | 1 | Agree |
| Was there clear reporting of the demographics of the participants in the study? | 1 | 1 | Agree |
| Was there clear reporting of clinical information of the participants? | 1 | 1 | Agree |
| Were the outcomes or follow-up results of cases clearly reported? | 1 | 1 | The ERG agrees that outcomes of case series studies have been clearly reported, however long-term follow-up data have not been provided for the patients in the case series studies |
| Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 1 | 1 | Agree |
| Was statistical analysis appropriate? | 1 | 1 | Agree |
| Score | 9 | 10 | |

CSR=clinical study report; ERG=evidence review group
Source: CS, Appendix 4

## *11.2 Study characteristics*

The study characteristics of, the HLSTM02 and the HLSTM04 case series studies are shown in Table 9.

### *11.3 Patient characteristics*

The demographic characteristics of the patients in the HLSTM02 and the HLSTM04 case series studies are presented in Table 11. Clinical advice to the ERG is that the patients in the studies are representative of patients with moderate to severe LSCD who would be treated in the NHS.

Table 41 Patient baseline characteristics in the HLSTM02 and HLSTM04 case series studies

| | **HLSTM02 N=29** | **HLSTM04 N=15** |
|---|---|---|
| Mean age (SD) | 45.8 (17.4) | 46.5 (16.9) |
| Age range | 8 to 71 | 21 to 79 |
| Male n (%) | 22 (75.9) | 14 (93) |
| Time from injury to treatment with Holoclar | 14.1 years | |

Source: CSR for HLSTM02 and HLSTM04

## 11.3.1 HLSTM02

The HLSTM02 case series study included 29 patients with a follow-up of 12 months. The primary aim of the study was to determine the safety of Holoclar in terms of the number of subjects who experienced AEs and the number of AEs. A total of 46 AEs were reported in 19 patients (65.5%). The company reports that eye disorders were the most common group of AEs. Five SAEs were reported in three patients (10.3%) and three of these SAEs in two patients were considered to be treatment-related.

A secondary endpoint in this study was the outcome of the Holoclar transplantation in terms of success or failure based on independent masked assessment. According to the independent assessor, success was achieved in 19 patients (65.5%; 95% CI: 48.2 to 82.8%), failure was reported for six patients (20.7%) and information was missing for four patients (13.8%).

## 11.3.2 HLSTM04

The primary efficacy endpoints of the study were to evaluate outcome of Holoclar transplantation, the presence and severity of clinical symptoms before and after transplant and best-refracted VA before and after treatment with Holoclar. Overall, success was reported in nine patients (60%) at the time of the 90 day follow-up and these results were maintained until the final visit (mean 217 days (85 to 777 days). Due to a large amount of data being missing at baseline (60%) it was difficult to assess the data on the presence of clinical symptoms. The results demonstrate significant improvements in VA at both day 90 and the last visit despite majority of the study population exhibiting stromal scarring.

# National Institute for Health and Care Excellence

# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

## Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns ID899

You are asked to check the ERG report from Liverpool Reviews & Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 21 October 2016** sing the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

## Issue 1 Inaccurate description of the marketing authorisation and therapeutic indication for Holoclar

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| The ERG states, "that the European Medicines Agency (EMA) marketing authorisation for Holoclar specifies its use in patients with moderate to severe LSCD due to ocular burns; there is no specific reference to Holoclar use in unilateral LSCD or bilateral LSCD".<br><br>(Section 2.2.2, page 24) | The European Medicines Agency (EMA) marketing authorisation for Holoclar specifies its use for treatment of adult patients with moderate to severe limbal stem cell deficiency, ***unilateral or bilateral***, due to physical or chemical ocular burns (see Holoclar SmPC, section 4.1 Therapeutic Indications). | To correct a factual error regarding the licensed indication of Holoclar and the recommended target population that is specified in the SmPC for Holoclar.<br><br>This has significant impact on the understanding of the place of Holoclar in the treatment pathway of the LSCD, especially in relation to CLAU which is not used/cannot be used to treat patients with bilateral LSCD. | This is a factual error.<br><br>The ERG report has been amended as suggested. |

## Issue 2 Inaccurate statement of the follow-up period for studies HLSTM01 and HLSTM02

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| The ERG states that, "the duration of follow-up for the HLSTM01 and the HLSTM02 case series studies is 1 year".<br><br>(Section 4.4, page 44) | Whilst the main endpoints were measured at 12 months, the duration of the follow-up period for both studies was up to 10 years (and up to 14.5 years as published in Pellegrini 2013). | To correct a factual error regarding the duration of the follow-up period in studies HMSTM01 and HLSTM02.<br><br>In addition, there is a high degree of overlap between the patient population reported in the study by Pellegrini 2013 and the patient populations of HLSTM01 and HLSTM02. Out of the 152 patients included in the Pelligrini publication, 133 are included in HLSTM01 and HLSTM02 and provide follow-up | The ERG agrees that the main endpoints of the HLSTM01 and HLSTM02 case series studies were measured at 1 year. The ERG notes that patients in the Pellegrini 2013, Rama 2001 and Rama 2010 studies were followed up for a mean of 8.4 years, 27 months and 2.91 years respectively.<br><br>The ERG report has been amended to reflect this. |

| | | | |
|---|---|---|---|
| | | data for a period of up to 14.5 years.<br>This has an impact on the understanding of the data set available to support long-term outcomes with Holoclar. | The ERG notes that the main endpoints for the HLSTM01 and the HLSTM02 case series studies are measured 1 year. Patients were followed up for a mean duration of 8.4 years,[45] 27 months[47] and 2.91 years.[48] |

## Issue 3 Inaccurate description as to the plausibility of management of patients with failed Lr-CLAL

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG considers it "implausible that patients with unilateral LSCD who fail after Lr-CLAL are not offered a second procedure".<br>(Section 1.6, pages 16-17 and section 6.3, page 102) | It is extremely unlikely that patients with unilateral LSCD who fail after Lr-CLAL would be offered a second procedure. | It is unreasonable (and potentially unethical) to expect a living related donor to donate large portions of conjunctivolimbal tissue from both of their eyes (conjunctivolimbal tissue cannot be harvested from the same eye twice), as would be required for repeat lr-CLAL. It is extremely unlikely that repeat lr-CLAL would be considered or undertaken.<br>Furthermore, if Lr-CLAL has failed, KLAL from a non-HLA matched cadaveric donor is also (more) likely to fail. In addition, there may be clinical reasons why Lr-CLAL was initially used in preference to KLAL, e.g. the risks to the patient of the associated higher levels of immunosuppression required for KLAL making the patient unsuitable for KLAL.<br>This has impact on the ERG's conclusions as to the cost- | This is a matter of opinion and not an issue of factual accuracy. In the ERG report results are presented with and without a second procedure after Lr-CLAL.<br>No change has been made to the ERG report. |

| | | | |
|---|---|---|---|
| | | effectiveness of Lr-CLAL (and KLAL). | |

## Issue 4 Inaccurate description of the number of biopsies required for retreatment with Holoclar

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG states, "the Holoclar transplant itself can be carried out up to three times even if the first and second transplants fail. This means that a total of six biopsies could be required from a damaged eye that may only have 1-2mm$^2$ of undamaged limbus".<br><br>(Section 3.2, page 33) | Deletion of the sentence that reads "This means that a total of six biopsies could be required from a damaged eye that may only have 1-2mm$^2$ of undamaged limbus" and revision of the conclusions drawn by the ERG based on this inaccuracy. | It is incorrect for the ERG to conclude that six biopsies are required for retreatment with Holoclar and it is unclear how this figure has been derived by the ERG.<br><br>As explained in the company submission (sections 2.1 and 3.1.4), unlike CLAU or Lr-CLAL where two large sections of conjunctivolimbal tissue are harvested for transplantation, only one single and much smaller biopsy is required for Holoclar. Furthermore, for Holoclar the patient's stem cells are expanded (i.e. cell replication at the manufacturing site to generate a much larger number of stem cells than was originally removed at biopsy), the expanded cell suspension is cryopreserved prior to transplantation and some of the patients expanded cells are retained at the manufacturing site in a frozen state. It is therefore possible to manufacture a second Holoclar without the need for a repeat biopsy.<br><br>This has impact on the ERG's conclusions about retreatment with | It is stated in Table 50 of the company submission (CS) that 90% of biopsies for Holoclar are successful. In the company model this translates into 10% requiring a second biopsy. In the company model, patients are allowed three attempts with Holoclar, each time potentially having two biopsies but at least one. Implicitly in the company model therefore a patient can have up to six biopsies.<br><br>No change has been made to the ERG report. |

| | | | |
|---|---|---|---|
| | | Holoclar and treatment with Holoclar in both eyes. | |

## Issue 5 Inaccurate description of the clinical effectiveness of Holoclar when used to treat bilateral LSCD

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG states, "that there are plausible clinical reasons as to why Holoclar may not be as effective when used to treat bilateral LSCD compared with use in unilateral LSCD".<br><br>(Section 3.3, page 32 and Section 6.3,page 101) | This is no evidence and no plausible clinical reasons to suggest that Holoclar may not be as effective when used to treat bilateral LSCD compared with use in unilateral LSCD. | The only requirement for the use of Holoclar is that a minimum of 1-2 $mm^2$ of undamaged limbus is available for biopsy. This is irrespective of whether the biopsy is taken from a healthy or affected eye. Given that the biopsy is of *undamaged limbus*, the status of the remaining portion of the eye not included in the biopsy has no relevance or influence on the ability to manufacture Holoclar.<br><br>Holoclar is an advanced therapy medicinal product manufactured to GMP standards. As part of the manufacturing process there are very strict quality control and batch release testing procedures in place that ensure release of each batch of Holoclar (individual to the patient) can only take place if these predefined manufacturing standards are met. These standards include tests for potency, as described in section 2.1 of the company submission, where determination of $p63^{bright}$ is used as a potency test in | In response to clarification question B1, the company stated: *"It is not possible to indicate whether patients included in the HLSTM01 study had unilateral or bilateral limbal stem cell deficiency as this was not recorded in the CRF or otherwise reported in the HLSTM01 study. However, what is known is that only one patient with bilateral LSCD was treated with Holoclar in both eyes"*<br><br>The ERG is uncertain how the company is now able to identify 13 patients with bilateral LSCD from the dataset.<br><br>The company does not provide a separate analysis of the 13 patients and nor does it provide analysis for the one patient who had the procedure in both eyes.<br><br>The ERG presented several clinical reasons why Holoclar |

| | | | |
|---|---|---|---|
| | | the release specification. P63$^{bright}$t is also known to be a biomarker for efficacy. The same manufacturing and batch release standards are used regardless of whether the biopsy is taken from a healthy or an affected eye. Therefore the quality of the Holoclar product is consistently high and standardised across both patient subgroups.<br><br>In terms of the clinical effectiveness of Holoclar, whether the contralateral eye is affected or unaffected has no impact on the ability to treat an affected eye with Holoclar (unlike CLAU) or on the clinical outcomes seen in an eye treated with Holoclar. Indeed, the clinical- and cost-effectiveness of Holoclar in both groups of patients have already been presented in the company submission. Of the patients included in the HLSTM01 study, 13 patients had bilateral LSCD. Of these, 12 patients had one eye treated and 1 patient had both eyes treated as part of HLSTM01.<br><br>This has impact on the ERG's conclusions about the clinical effectiveness of treatment with Holoclar in bilateral LSCD. | may not be as effective in patients with bilateral LSCD when compared with patients with unilateral LSCD.<br><br>Clinical advice to the ERG supported the reasons given and agreed that treatment in bilateral patients should not be assumed equally as efficacious as in unilateral patients.<br><br>No change has been made to the ERG report. |

## Issue 6 Inaccurate description of the manufacturing process and costs of Holoclar

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG states that "the company presents no evidence on the success rates with frozen and defrosted grafts nor does it indicate what the costs of this option would be".<br><br>(Section 3.2, page 33) | As described in section 2.1 of the company submission, ALL Holoclar treatments are undertaken with frozen and thawed product. Cryopreservation following cell expansion is part of the manufacturing specification of Holoclar, which is controlled and standardised within strict GMP quality assurance parameters. In all cases, a proportion of the expanded cells are retained at the manufacturing site.<br><br>As this is part of the standard GMP manufacturing process, the costs of this is included in the stated list price. | To correct a factual inaccuracy regarding the manufacturing process and cost of Holoclar.<br><br>This has impact on the ERG's conclusions about treatment with Holoclar in both eyes. | The CS does not state that cells from a biopsy *in addition to those used in the transplant* are frozen, stored and defrosted should transplant fail. Indeed, in the company model if Holoclar transplant fails a new biopsy is required. The costs of storage of a graft and success rates after the graft has been frozen for some time are not considered. However, the ERG agrees that the statement in Section 3.2 is potentially misleading and so the wording has been changed to:<br><br>"the company presents no evidence on the success rates with grafts that have been stored 'in reserve' nor does it indicate what the costs of this option would be" |

## Issue 7 Update available in relation to the UK Prix Galien award

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG states, "Holoclar has been named one of four finalists shortlisted for an award in innovation and research – the UK Prix Galien Orphan Product award. A Prix Galien award is widely regarded as the highest distinction to bestow upon a pharmaceutical product."<br>(Section 2.4, page 27) | Holoclar has now won the UK Prix Galien Orphan Product award. | This prize was awarded on 21st September 2016.<br>This updated information may have significant impact on the way in which the Appraisal Committee considers the level of innovation of Holoclar and how the innovation of Holoclar is thought of in the external environment and by society. The Prix Galien is widely regarded as the highest distinction to bestow upon a pharmaceutical product and is awarded by a distinguished and independent panel of industry and other experts, including senior representatives of NICE and the MHRA. | This is not an issue of factual accuracy. No change has been made to the ERG report. |

## Issue 8 Incorrect assumption that autologous serum eye drops would be used with Holoclar

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The assumed use of autologous serum eye drops with Holoclar post-operatively.<br>(Section 5.4.4, page 88) | Autologous serum eye drops should not be included in the model for Holoclar treatment post-operatively, unlike CLAU, Lr-CLAL or KLAL where autologous serum eye drops are used routinely for a post-operative period of 3 months. The addition of this cost for Holoclar should be removed. | Autologous serum eye drops were not used post-operatively in any patients in the HLSTM01 or any other Holoclar study. The use of autologous serum eye drops is not part of the protocol for HLSTM01, HLSTM02 or HLSTM04 or described in any of the published studies of | The use of autologous eye drops is uncertain in all procedures. The ERG considered that consistency across procedures was paramount and as such included the cost for Holoclar whilst pointing out that either |

| | | | |
|---|---|---|---|
| | | Holoclar and autologous serum eye drops were not recorded as having been used as a concomitant treatment in study HLSTM01, HLSTM02 or HLSTM04.<br><br>Furthermore, autologous serum eye drops are not included in the approved Holoclar Marketing Authorisation/SmPC and should not be used with Holoclar. Indeed, section 6.2 (Incompatibilities) of the approved Holoclar SmPC states that "There have been no formal compatibility studies with Holoclar therefore this medicinal product should not be used with other medicinal products during the post-surgical period until the corneal epithelium integrity is fully restored. Exceptions include non-topical antibiotics for prophylaxis and corticosteroids during the immediate post-operative period."<br><br>This error is inconsistent with the use of Holoclar and has artificially increased the cost of Holoclar. | adding the cost to Holoclar or subtracting it from the other procedures should essentially have the same impact on the ICERs.<br><br>No change has been made to the ERG report. |

## Issue 9 Percentage of patients with successful transplants at 12 months

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG state, "However, the models assume that the 86.8% of patients that have successful transplants at 12 months are | It is correct that the base case assumed a zero probability of additional failure post 1 year for both Holoclar and CLAU. However, whilst we did not explicitly include an automated option for non-zero | Correction of factual error that implies the model is insufficiently flexible to address possible future failure of Holoclar and CLAU. | The model does allow an annual failure rate to be modelled post 12 months. However, what the model |

| | | | |
|---|---|---|---|
| considered to have successful transplants for life. The same assumption is made for Holoclar patients who have stable transplants at 12 months. The models cannot be changed to allow failure rates at 10 years without completely restructuring them and this modification is beyond the remit of the ERG."<br><br>(Section 1.6, page 16 and Section 5.4.1, page 77) | probabilities of post 1 year failure for Holoclar or CLAU, the change could be readily made by simply changing the values for the " in the "survival probabilities" (e.g. Trial_Hol_Pr_12monthplus_Stab) or "Developer 1" (e.g. Pr_Hol_Stab12plus_Op1) sheets. The transition probabilities matrix for the model then should automatically update with these values. No structural changes to the model would be required. | Although of minor impact, this does allow the ERG to further examine failure rates at 10 years. | does not allow is differential failure rates by year post 12 months. This is important if grafts that are stable at 12 months start failing at five years.<br><br>The wording on page 77 of the ERG report has been changed to:<br>"However, the models assume that the 86.8% of patients that have successful transplants at 12 months are considered to have successful transplants for life. The same assumption is made for Holoclar patients who have stable transplants at 12 months. The models cannot be changed to allow failure rates by year after 12 months without modifications beyond the remit of the ERG."<br><br>The ERG was unable to identify any relevant text in Section 1.6 of the ERG report. |

STA REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns ID899

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/148/05

Completed 26th October 2016

DOES NOT CONTAIN COMMERCIAL OR ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains erratum in respect of the ERG report following the factual accuracy check by Chiesi UK Ltd.

Changes made to the original text in the ERG report are highlighted in grey.

Holoclar to the hospital where it is implanted in the patient's eye. Transplantation must take place within 36 hours of Holoclar being despatched by the manufacturer to the hospital.

The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium. Holoclar is the first advanced therapy medicinal product (ATMP) containing stem cells to receive a Marketing Authorisation in Europe.

The company states (CS, p36) that in the UK, treatment with Holoclar will be carried out in two specialist ophthalmology centres (one in London and one in Newcastle). The company explains that limiting the number of treatment centres will ensure that the requisite surgical skills and experience in the treatment of the rare condition of LSCD will be developed and maintained. The company also states that Holoclar is to be commissioned by NHS England specialised services

The company states (CS, p58 and p59) that the introduction of Holoclar will not change the current treatment pathway within the NHS and considers Holoclar to be an alternative treatment option for the groups of patients listed in Table 2. TEXT REMOVED

Table 2 Patients with moderate to severe LSCD who would be treated with Holoclar

| **Patient subgroup** | |
|---|---|
| **Unilateral LSCD** | **Bilateral LSCD**<br>(Minimum of 1-2mm$^2$ of undamaged limbus) |
| Patients who are unsuitable for treatment with CLAU or who are unwilling to undergo CLAU because of concerns about damage to their donor eye | As an alternative to Lr-CLAL in patients without an available and/or willing live-related donor |
| Failed treatment with CLAU (once-only treatment) | Patients who are unsuitable for topical and systemic immunosuppression (immunosuppressive treatment is mandatory following Lr-CLAL and KLAL transplantation) |
| | Patients who require a successful treatment outcome beyond 3 to 5 years |

CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; Lr-CLAL= CLAL from a live related donor; LSCD=limbal stem cell deficiency
Source: CS, p58

The ERG notes from Table 2 that the company is suggesting that for bilateral LSCD, the duration of successful treatment with conjunctival limbal allograft form a living relative (Lr-CLAL) and KLAL is between 3 and 5 years. Clinical advice to the ERG is that treatment

- be more difficult to locate and extract healthy limbal cells from a damaged eye than from a healthy eye.
- The company has assumed that the same number of biopsies can be taken from a healthy eye as from a damaged eye. Whether using a damaged or undamaged eye, the company states that there is a 10% chance that the first biopsy will fail. The company goes on to state that the Holoclar transplant itself can be carried out up to three times even if the first and second transplants fail. This means that a total of six biopsies could be required from a damaged eye that may only have 1-2mm$^2$ of undamaged limbus. The ERG does not consider this to be plausible. By default, that means that, even if the success rate per transplant is the same, overall efficacy of bilateral transplantation will be lower than the efficacy of unilateral transplantation simply due to the lower number of transplants that could be performed in patients undergoing bilateral intervention.

The company also states that multiple grafts can be grown from a single biopsy and that these can be frozen and used should the initial graft fail. This would potentially allow for only a single biopsy to be taken from a damaged eye and be used bilaterally if required. However, the company presents no evidence on the success rates with grafts that have been stored 'in reserve' nor does it indicate what the costs of this option would be. As such, the ERG considers that this approach should not be considered in the CS and the company rightly does not include it as an option in the economic model.

Given the clinical reasons to doubt the equal efficacy of using Holoclar unilaterally and bilaterally, and the absence of supportive clinical effectiveness evidence available, the ERG considers the assumption of equal efficacy to be unfounded.

## *3.3 Intervention*

Holoclar has been licensed in Europe since February 2015 for the treatment of adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2mm$^2$ of undamaged limbus is required for biopsy. The marketing authorisation is conditional on the company providing the results from an on-going prospective, European, uncontrolled phase IV study known as HLSTM03[50] (or HOLOCORE). The company expects the results of the study[50] to be available in 2020.

A regimen of post-implantation treatment is stipulated in the EMA marketing authorisation[13] for Holoclar. The regimen includes antibiotics (doxycycline or amoxicillin), prednisone, topical corticosteroids and dexamethasone eye-drops. Specific details are provided in the CS (p36) and in the SmPC.[30]

Table 10 Company's assessment of the risk of bias for the HLSTM01 case series study with ERG comment

| JBI checklist criteria | Company assessment | ERG comment |
|---|---|---|
| Were there clear criteria for inclusion in the case series? | 1 | Agree |
| Was the condition measured in a standard, reliable way for all participants included in the case series? | 1 | Agree |
| Were valid methods used for identification of the condition for all participants included in the case series? | 1 | Agree |
| Did the case series have consecutive inclusion of participants? | 1 | The ERG is unclear how the company has assessed this criterion as sufficient information is not provided in the protocol or CSR to assess whether the case series studies have consecutively included participants or not |
| Did the case series have complete inclusion of participants? | 0 | Agree |
| Was there clear reporting of the demographics of the participants in the study? | 1 | Agree |
| Was there clear reporting of clinical information of the participants? | 1 | Agree |
| Were the outcomes or follow-up results of cases clearly reported? | 1 | The ERG agrees that outcomes of case series studies have been clearly reported, however sufficient long-term follow-up data have not been provided for the patients in the case series studies |
| Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 1 | Agree |
| Was statistical analysis appropriate? | 1 | The ERG disagrees that the statistical analysis was appropriate for HLSTM01 as hypothesis testing has been carried out |
| Score | 9 | |

CSR=clinical study report; ERG=evidence review group
Source: CS, Appendix 4

## *4.4 Study characteristics*

The study characteristics of the HLSTM01 case series studies are shown in Table 9. The ERG is aware that the number of patients included in the HLSTM01 study (n=104) is substantial, given the rarity of the condition. As noted in Section 4.2.1 of this ERG report, the HLSTM01 case series study was conducted in 106 patients. The 104 patients in the ITT population were those who had received treatment with Holoclar and had a control visit at least 6 months after transplantation. The ERG notes that the main endpoints for the HLSTM01 and the HLSTM02 case series studies are measured 1 year. Patients were followed up for a mean duration of 8.4 years,[45] 27 months[47] and 2.91 years.[48]

The ERG notes the numerous data quality issues related to study design discussed in Section 4 and considers that all of the included studies in the systematic review are equally flawed. However, in contrast to the company's statement that it was inappropriate to pool the data from the comparator studies due to parameter heterogeneity, pooled estimates of the effectiveness data are used in the base case economic models. It is not clear whether this is a pooling of data from specific studies of patients with ocular burns, or is a pooling of data from all studies and all patients. However, as the individual studies have very small sample sizes, the ERG considers it doubtful that selection of any one study will produce more robust results than the pooled analysis. However, the weak evidence base from which the comparator effectiveness is drawn needs to be taken into account when assessing the robustness of the ICERs generated by the company models.

Clinical advice to the company is that Lr-CLAL and KLAL procedures all fail by 5 years. However, the company models suggest that 32.2% of patients with Lr-CLAL and 24.2% of patients with KLAL have a stable first transplant at 5 years. Whilst this could mean that the success rates of Lr-CLAL and KLAL are overstated in the company models, this assumption is consistent with the published studies[11,26,27,49,51,65,66,68,72,77-81] identified in the CS, if not with clinical opinion.

Similarly, clinical advice to the company is that 30% of CLAU transplants fail by 10 years. However, the models assume that the 86.8% of patients that have successful transplants at 12 months are considered to have successful transplants for life. The same assumption is made for Holoclar patients who have stable transplants at 12 months. The models cannot be changed to allow failure rates by year after 12 months without modifications that are beyond the remit of the ERG. In any case, the evidence to support the restructure would only be from a single clinical opinion on CLAU and there is no evidence on 10-year survival for Holoclar beyond one patient from the HLMST01 case series study. The ERG considers it an inherent weakness in the models that longer term (post-12 months) failure rates cannot be explored. If transplant failure occurs post 12 months for CLAU and Holoclar, then the ICERs per QALY gained for both treatments compared to the alternative procedures would increase. The impact on the ICER per QALY gained between Holoclar and CLAU of failure post 12 months would be dependent on the relative failure rate between the two procedures, which is unknown.

The ERG requested patient level data from the HLMST01 case series study that was used to generate the clinical effectiveness results for Holoclar. The ERG considers that a simpler analysis of the data could have been performed than was carried out by the company. The company could have looked at the success rate associated with removing disfigurement and the average line increase in VA – especially given that improvement in VA was arbitrarily

ID899 STA Ex vivo expanded autologous human corneal epithelial cells Confidential appendix

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns – ID899

## Confidential appendix: ERG economic analysis of ex vivo expanded autologous human corneal epithelial

This report was commissioned by the NIHR HTA Programme as project number 15/148/05

Completed 21st February 2017

CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

# ALL TABLES IN THIS APPENDIX ARE CONFIDENTIAL

Following a second submission from the company in February 2017, NICE requested that the ERG provide the adjustments to the company base case results for ex vivo expanded autologous human corneal epithelial at a list price of £80,000.

In this appendix, the ERG has applied the same adjustments as made to the original company base case analysis with ex vivo expanded autologous human corneal epithelial with a PAS discount applied.

**Table 1 ERG adjustments to company base case: Holoclar versus CLAU (unilateral model)**

| *Scenario/ERG amendment* | Holoclar | | CLAU | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| ***A. Company's base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of autologous serum eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group

**Table 2 ERG adjustments to company base case: Holoclar versus Lr-CLAL (unilateral model)**

| *Scenario/ERG amendment* | Holoclar | | Lr-CLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| ***A. Company's base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R6) Two attempts at Ir-CLAL | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **F. All suggested changes from ERG (R1-R6)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **G. All suggested changes from ERG but continued use of autologous serum eye drops for flare up (R1-R4, R6)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group

**Table 3 ERG adjustments to company base case: Holoclar versus KLAL (unilateral model)**

| *Scenario/ERG amendment* | Holoclar | | KLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| ***A. Company's base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group

**Table 4 ERG adjustments to company base case: Holoclar versus BSC (unilateral model)**

| *Scenario/ERG amendment* | Holoclar | | BSC | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| ***A. Company's base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group

**Table 5 ERG adjustments to company base case: Holoclar versus Lr-CLAL (bilateral model)**

| *Scenario/ERG amendment* | Holoclar | | Lr-CLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| ***A. Company's base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group

**Table 6 ERG adjustments to company base case: Holoclar versus KLAL (bilateral model)**

| *Scenario/ERG amendment* | Holoclar | | KLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| ***A. Company's base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group

**Table 7 ERG adjustments to company base case: Holoclar versus BSC (bilateral model)**

| *Scenario/ERG amendment* | Holoclar | | BSC | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £/QALY | Change from base case |
| **A. Company's base case** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | |
| R1) Use of Brown 2003 VA utility values | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R2) ERG preferred decrement for disfigurement | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R3) 3.5% discount rate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| R5) Autologous serum eye drops not used in flare ups | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare ups (R1-R5)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group