For committee and public handouts, no confidential information

Lead team presentation
Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns – STA

1st Appraisal Committee meeting

Clinical Effectiveness

Committee C

Lead team: Peter Selby, Judith Wardle, Paul Tappenden

ERG: Liverpool Reviews & Implementation Group

NICE technical team: Irina Voicechovskaja, Carl Prescott, Frances Sutcliffe

16 March 2017

Key issues – clinical

- Has the clinical effectiveness of Holoclar been adequately demonstrated?
  - Clinical effectiveness from case-series data
  - Company did 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 England?
  - Only 1 patient had bilateral disease – can any judgements be made about bilateral clinical effectiveness?
  - Do clinical results show a long-term durability of response?
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- Should comparator data be pooled?
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Definitions

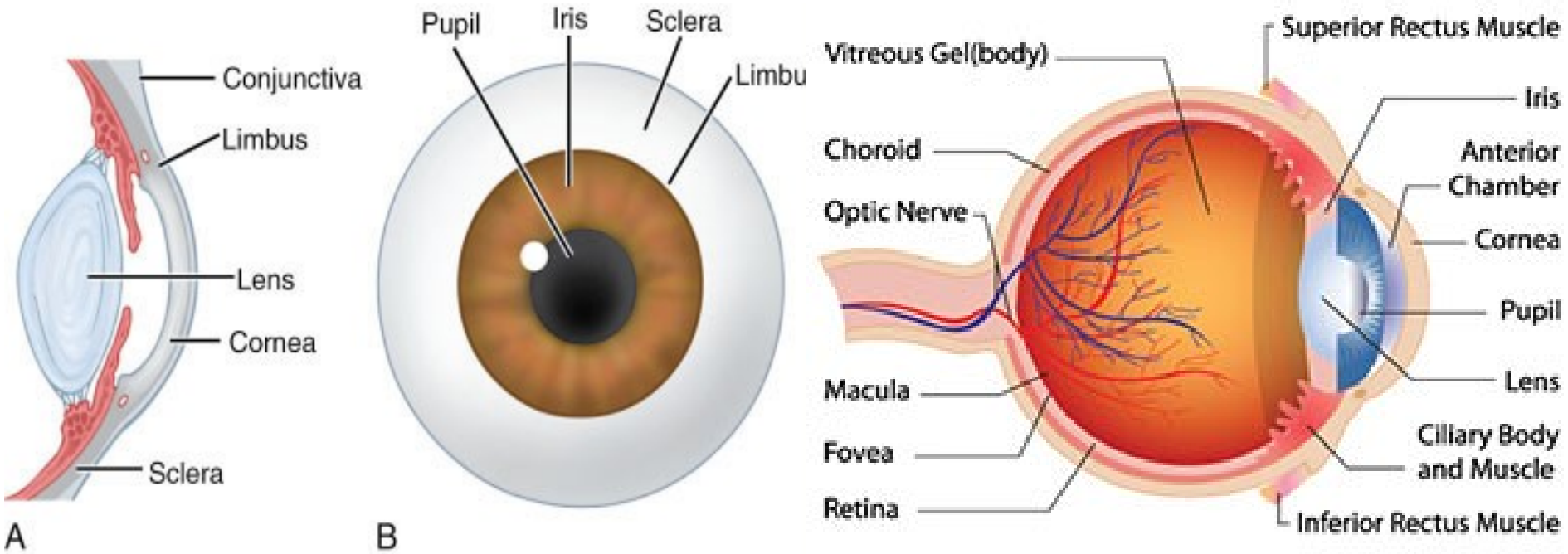
Limbal stem cells	Stem cells for the cornea which reside at the corneoscleral limbus
Limbal stem cell deficiency (LSDC)	Limbal stem cells may be partially or totally depleted with resulting abnormalities in the corneal surface
Conjunctival limbal allograft (CLAL) Lr-CLAL Cd-CLAL	Transplanting limbal epithelial stem cells of the cornea from one person to another Conjunctival limbal allograft from a live related donor Conjunctival limbal allograft from a cadaveric donor
Conjunctival limbal autograft (CLAU)	Transplanting limbal epithelial stem cells of the cornea into a new position in the body of the same individual
Keratoplasty (corneal transplantation)	Cornea transplant or corneal graft
Keratolimbal allograft (KLAL)	Transplanting limbal epithelial stem cells of the cornea from a cadaveric donor
Oculoplastic interventions	Plastic and reconstructive surgery on the eye
Ex vivo expansion	Tissue grown in an external environment

NICE decision problem

	NICE scope and company submission	ERG
P	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	✓ Although no bilateral evidence presented
I	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	✓
C	<u>Unilateral LSCD</u> • Conjunctival limbal autograft (CLAU) • Best supportive care <u>Bilateral LSCD</u> • Conjunctival limbal autograft (CLAU) • Limbal epithelial stem cells allografts (CLAL, KLAL) • Best supportive care	+C/KLAL? ✓ ✓ ✗ ✓ ✓
O	• Clinical parameters of LSCD: stability and transparency of the corneal epithelium and superficial corneal neovascularisation • Symptoms of LSCD: pain, burning and photophobia • Visual acuity (the affected eye), Visual acuity (the whole person) • Adverse events • Health related quality of life (HRQoL)	✓

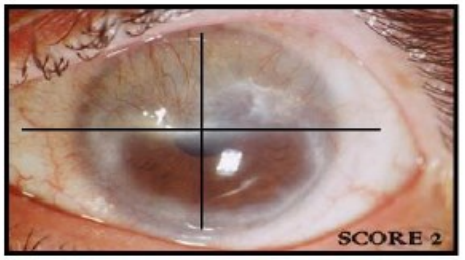
Disease background (1)

Figure: Anatomy of eye

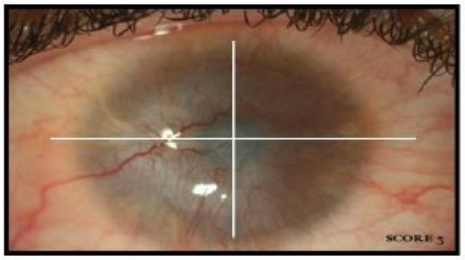


Source (anatomy of eye): Catapult cell therapy UK and medical dictionary

Figure: Moderate and severe LSCD



Moderate LSCD



Severe LSCD

Source (LSCD): company submission

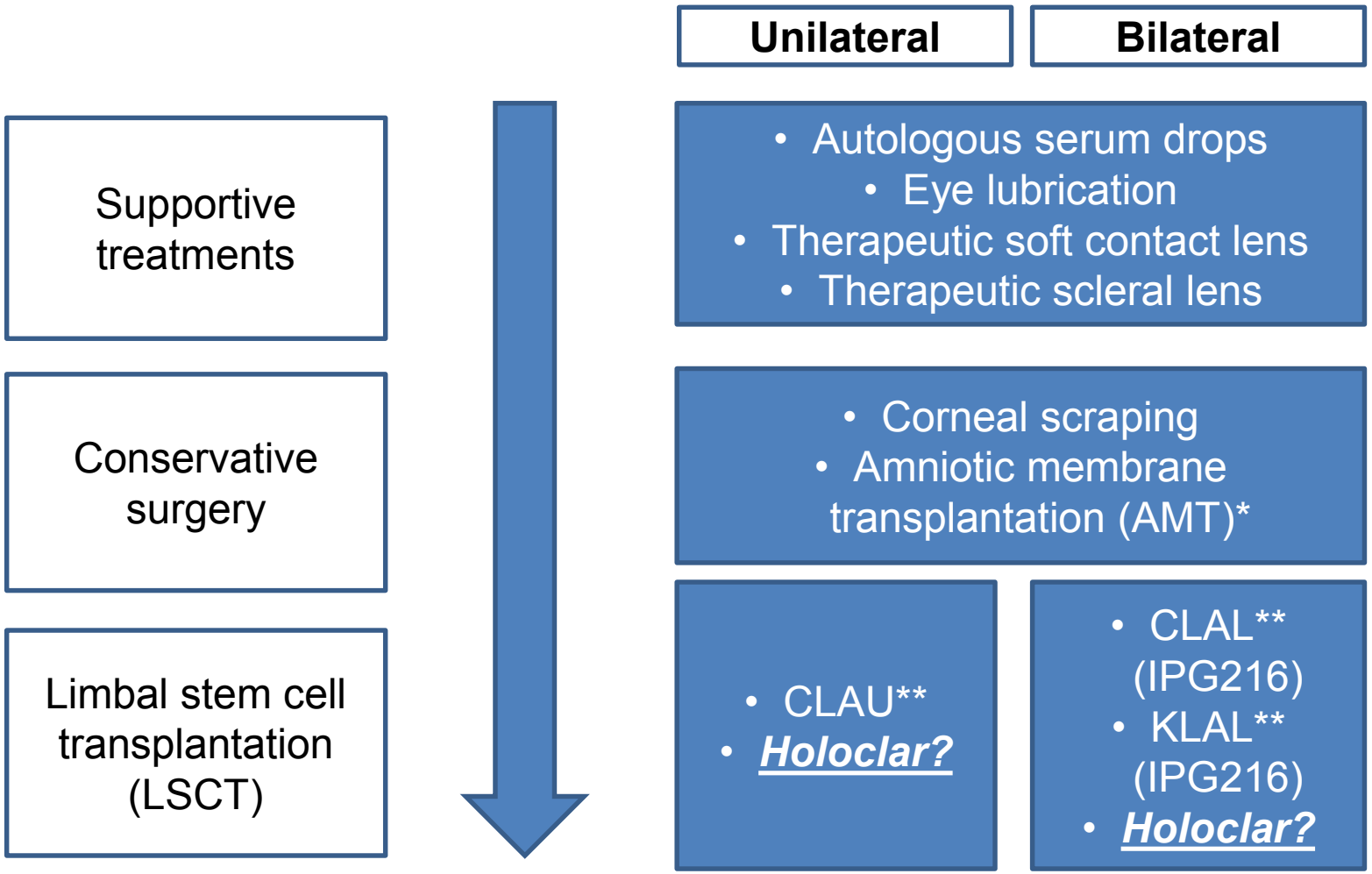
Disease background (2)

- Cornea – clear, rigid layer covering front of eye
- Cells constantly renewed and replaced by limbal stem cells
- LSCD caused by external (e.g. chemical or physical burns) or inherited damage, affects renewal and replacement
- Can cause excessive ingrowth of blood vessels (neovascularisation), opaque cornea, impaired vision, chronic pain/burning, photophobia
- Treatment aims to restore healthy surface
- Europe prevalence 0.3 per 10,000
- UK incidence from severe chemical corneal injury 0.02 per 100,000

Technology

Marketing authorisation (**conditional** on on-going phase IV prospective uncontrolled interventional study HLSTM03 (or HOLOCORE), expected 2020.	Treatment of adult patients 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), 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	Implant administered into eye.
Price	List price (all-inclusive e.g. staff training, shipment of biopsy etc.) is £80,000 (ex VAT) per treatment per eye. The company has agreed a patient access scheme with the Department of Health. The details of this patient access scheme are commercial in confidence.

Treatment pathway



*AMT can also be used in combination with LSCT

**May be combined with keratoplasty, with or without cataract surgery

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

Patient perspective

- No submission from patient experts
- The company presented testimonials form patients saying that the accident which led to the LDSC had a devastating effect on their lives, led to social isolation and inability to work.
- Patients stated that years of treatments with other drugs did not restore their sight and only reduced the pain.
- Treatment with Holoclar helped to restore patients' sight and visual appearance and get their life back; they were able to return to work and perform activities not possible after the accident.

Clinical evidence

- No RCTs for Holoclar or comparator treatments

Holoclar evidence:

- 3 x Italian case series, moderate to severe unilateral or bilateral LSCD due to ocular burns
- Main evidence HLSTM01 (n=104); supportive evidence HLSTM02 (n=29) and HLSTM04 (n=15)
- Primary outcome HLSTM01: transplant success (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 CLAL 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

ERG critique: Case series design

- Case series - descriptive observational study following group with same diagnosis or procedure over certain period
- Advantages:
  - high external validity if wide range of patients with different characteristics and co-interventions
  - relatively inexpensive
- Disadvantages:
  - **not designed to test hypothesis** of treatment efficacy
  - lack of randomisation and lack of comparison group
  - susceptible to selection and measurement bias
- HLSTM01 is flawed: **hypothesis testing was carried out**, lack of information about patient drop out, and missing data

Holoclar study characteristics

Company

- HLSTM01:
  - ITT population (n=104) treated with Holoclar and had control visit at least 6 months after transplantation
  - Mean age 47 (range 14 to 79), 77% male, 18.4 years from injury to treatment
- HLSTM01, 02 and 04:
  - All 3 studies (n=219). Data missing for 82 patients
  - Missing data "did not negate" conclusions because 25/82 included in 2 other studies, which had similar results to HLSTM01/02

ERG

- Given rarity of condition, study population substantial
- Population representative of those who would be treated in the NHS
- Risk of bias from missing data
- No. missing cases unclear, company calculation (135 + 82) =217, not 219
- Company unable to provide reasons for non-participation
- Attempt to address missing data bias insufficiently robust.

Source: ERG report, p.45

HLSTM01: study results

Primary outcome (transplant success):

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

Secondary outcomes:

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

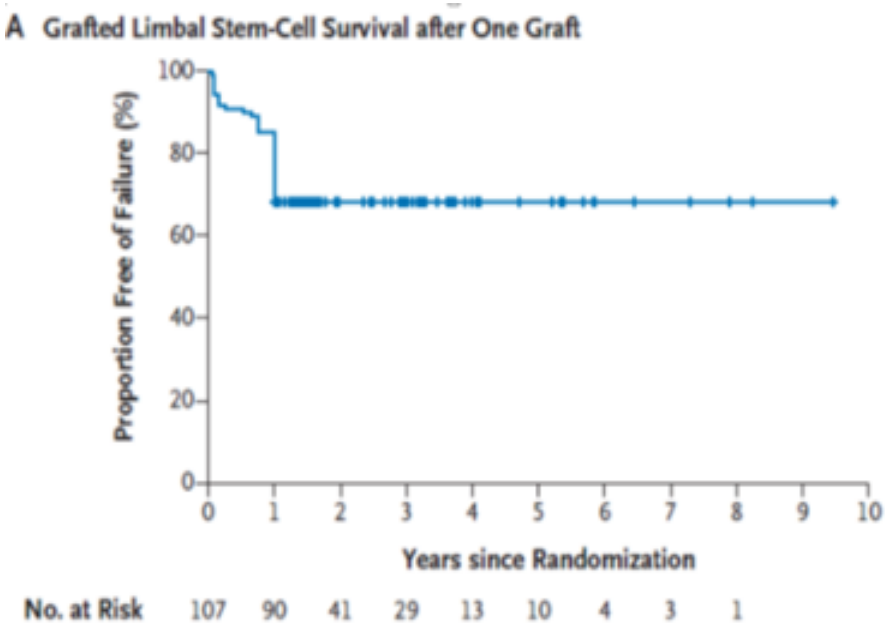
Table: HLSTM01 LSCD symptoms pre and 12 months post surgery

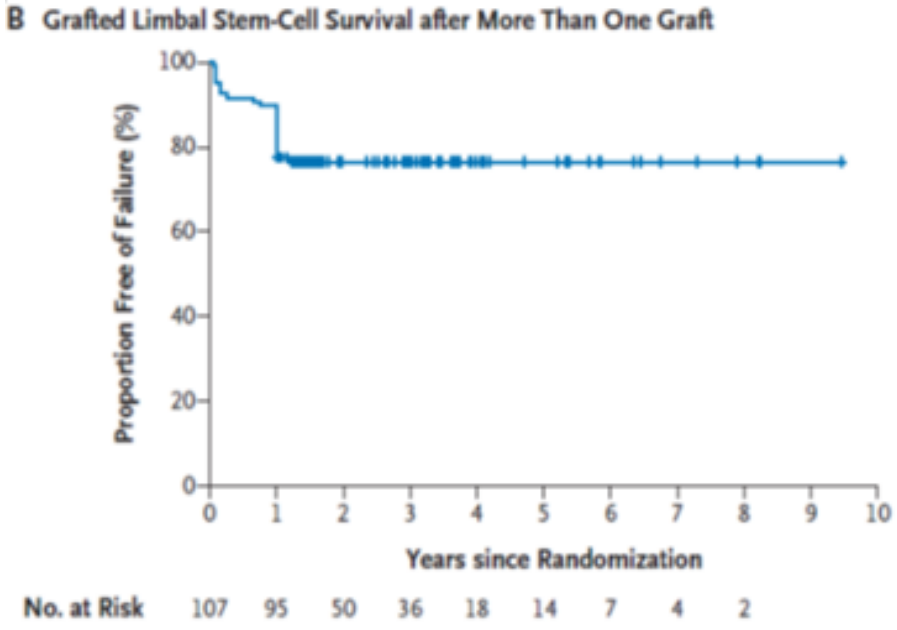
	Pre-surgical assessment n (%)	12 months post-surgery n (%)
Any symptoms	40 (38.5)	12 (11.5)
Pain	7 (6.7)	7 (6.7)*
Burning	30 (28.8)	7 (6.7)
Photophobia	35 (33.7)	8 (7.7)

* Based on 97 patients

Source: ERG report, p.46

Grafted limbal stem cell survival





Source: CS figure 12

Company

- Treatment failure: Presence of symptoms, recurrent epithelial defects, pannus and inflammation
- Kaplan-Meier survival analysis demonstrated that eyes considered successfully treated with Holoclar at 12 months remain successfully treated up to 10 years of follow-up.
- Effect is consistent both for single and repeat Holoclar treatment

ERG:

- Mean follow-up <3 years
- 17 people have follow-up >5 years; 1 person has follow-up >9 years

HLSTM01: ERG critique

- Clear and focused study question
- Well-defined inclusion and exclusion criteria
- No follow-up data >1 year for most
- Explores efficacy and safety, not patient satisfaction or mental wellbeing
- By reporting p-values and performing hypothesis testing, company implies Holoclar is successful in group of patients, but case series purpose descriptive only
- Evidence presented relevant to unilateral disease only, not bilateral
  - All, except one, had only 1 eye treated with Holoclar.
  - No clinical evidence to support Holoclar for 2 eyes.
  - Impossible to determine outcomes for bilateral patients receiving Holoclar in one or both eyes.

Comparator outcomes: Ocular stability

CLAU

- 11 studies, 5 exclusively in 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 2nd transplantation taken into account)
  - 5/6 (**83.3%**)
  - 15/16 (**94%**)
  - 6/6 (**100%**)

CLAL/KLAL

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

Comparator outcomes: Visual acuity

CLAU

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

CLAL/KLAL

- 15 studies; 4 exclusively in ocular burns. 3 reported visual acuity improvement:
  - 13/20 (**65%**),
  - 8/10 (**80%**)
  - 17/17 (**100%**)
- ERG: 1 study in unilateral LSCD, 1 in bilateral, and 1 mixed

Adverse events

	Holoclar (n=142)^	**CLAU***	**KLAL/CLAL***
Engraftment failure*	Not reported	10% (half persistent epithelial defect)	20% (half persistent epithelial defect)
Infection	1 case (0.7%)	0 to 20% grafted eyes 0 to <5% donor eyes	0 to 20% grafted eyes 0 to <5% donor eyes (Lr-CLAL)
Glaucoma	7 cases (4.9%)	5-10% patients	10% patients
Treatment failure (with recurrence of LSCD)	5 cases (3.5%)	20-30% patients within 10 years	All treatments will fail within 3-5 years

- * Based on clinical advice to the company
- ^ HLSTM01 and HLSTM02

Source: CS tables 16, 17; EPAR p.58

Comparator studies: ERG critique

- Studies largely retrospective, observational and small numbers of patients
- Company and ERG agree:
  - view results with caution because heterogeneous populations and interventions, and weak study design
  - pooling data inappropriate

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Cost Effectiveness

Committee C

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16 March 2017

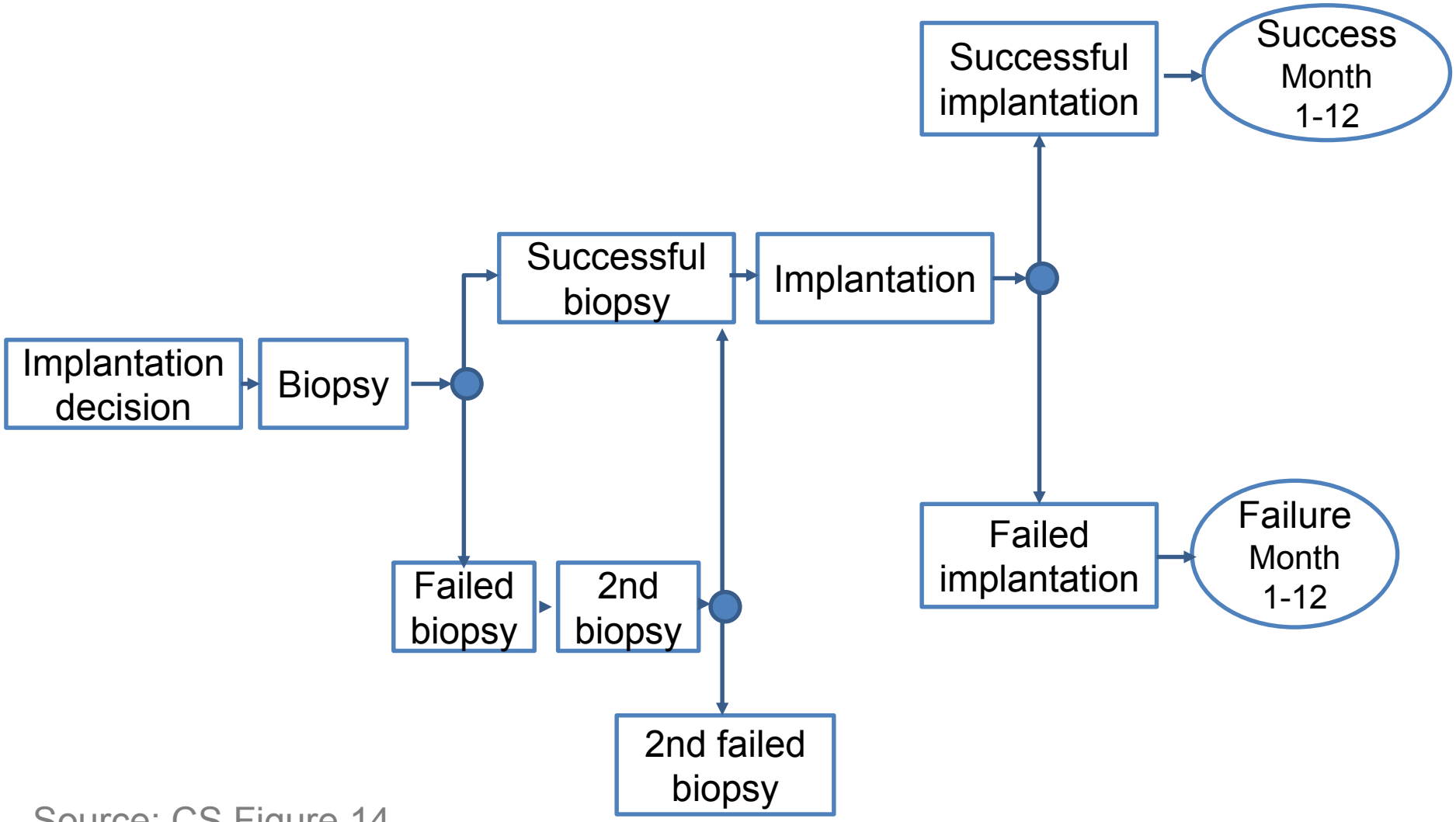
Key issues

- All treatments including Holoclar are dominated by CLAU (Holoclar less effective and more costly than CLAU)
- Effectiveness assumptions based on weak evidence (case series data)
- Bilateral effectiveness data available for only 1 patient
- Have the company used appropriate sources for utilities for this condition?
- Discount rate - 1.5% or 3.5%?
- Assumptions about autologous serum eye drops used for flare-ups and post-operatively
- Would patients be offered a second procedure after failure of CLAL?
- Are the company's assumptions about failure rates plausible?
- Innovation: Holoclar won UK Prix Galien Orphan Product award for innovation in Regenerative medicine – have all the benefits of treatment been quantified?

Company model

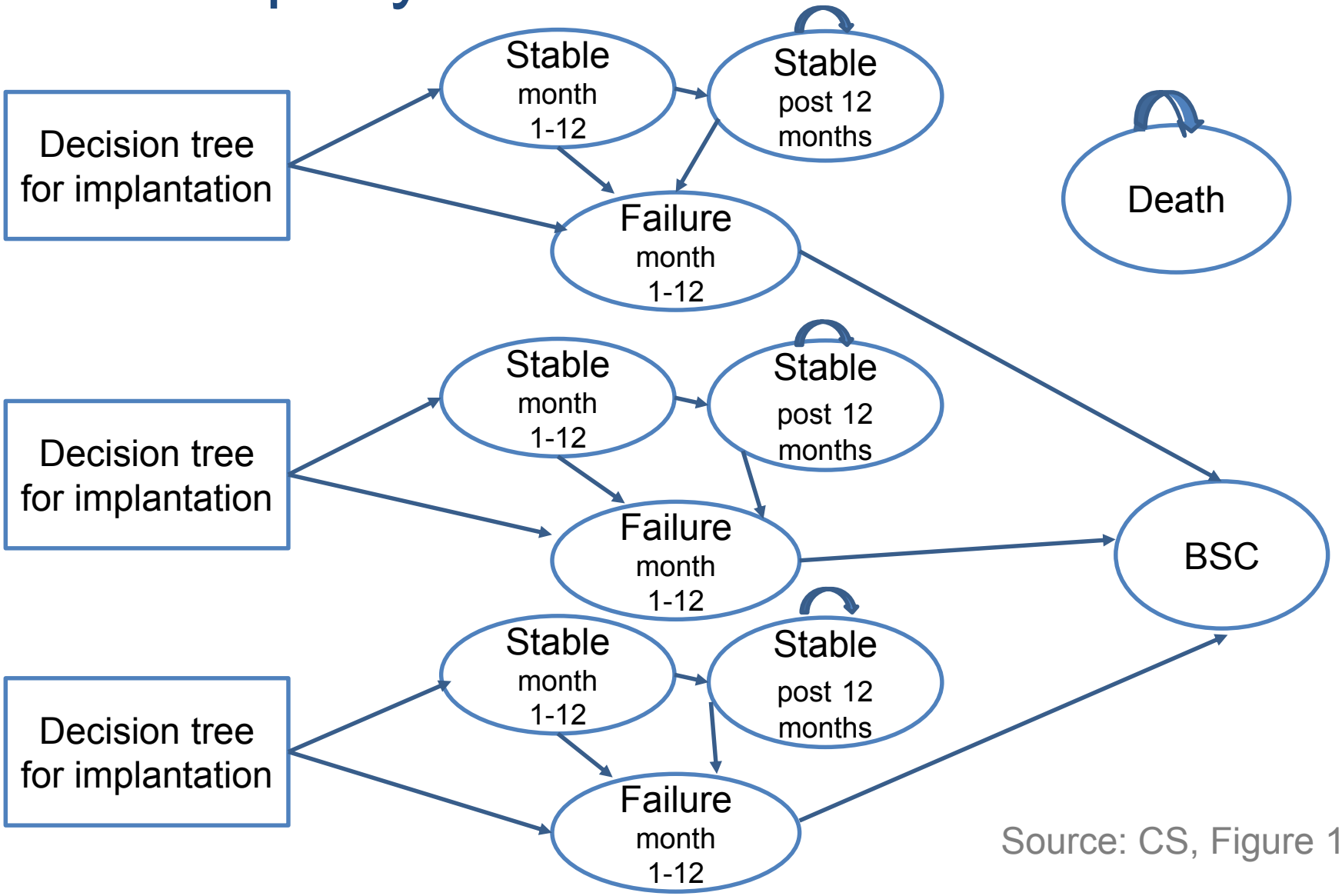
- 2 models: unilateral and bilateral. Initial phase – decision tree followed by Markov for long-term outcomes
- Population: male, mean age 46; VA=10
- Holoclar compared with:
  - conjunctival-limbal autograft (CLAU)
  - limbal epithelial stem cells allografts:
    - living-related conjunctival allograft (Lr-CLAL)
    - keratolimbal allogeneic transplantation (KLAL)
  - Best supportive care (BSC)
- Some patients with stromal scarring receive keratoplasty 1 year after successful Holoclar transplantation
- Perspective: NHS & PSS
- Time horizon: lifetime (50 years)
- Discount rate: 1.5%
- Model includes PAS for Holoclar

Decision tree: Unilateral LSCD



Source: CS Figure 14

Company's model: Unilateral LSCD



Source: CS, Figure 15

Note: Bilateral mode has similar structure but also includes additional year without treatment

Clinical effectiveness parameters

- Transplant success: restoration of stable cornea with little/no defects or blood vessels in cornea.
  - Holoclar – from HLSTM01 study
  - Comparators – pooled from literature
- Stromal scarring (SS): dependent on underlying rate in HLSTM01 (90%) and whether successful keratoplasty at year 1
- Outcomes according to treatment success/failure: Regression of HLSTM01 data to estimate:
  - VA score (dependent on transplant success and scarring)
  - Pain/burning/photophobia (dependent on transplant success and scarring)
  - Impact of keratoplasty on VA: Estimated from regression for scarring and keratoplasty (using scarring as a proxy for VA)

- Outputs of above regressions applied equally to Holoclar and comparators

Company's regressions to estimate VA, pain, and impact of keratoplasty on VA

(1) Probability of being in VA group post-success/failure & SS

- VA converted to 13-point scale (LP to 10/10 BCVA)
- Regression to estimate relationship between VA (dependent), transplant success, and stromal scarring
- Relationship assumed same as HLSTM01 at 12 months and remains constant over time
- Results for patients with 3 different baseline levels of visual acuity: good (top 25% of random effects model), poor (bottom 25%) and average

(2) Probability of pain/burning/photophobia post-success/failure & SS

- Regression to estimate relationship between 'any' pain/burning/photophobia (dependent variable), transplant success and stromal scarring
- Average patient only (less heterogeneity than VA)
- Scale of none, mild, moderate or severe

(3) Impact of keratoplasty on visual acuity

- Probability of SS from HLSTM01 used to indirectly estimate impact of keratoplasty on VA

Example output: 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

Health-related quality of life (HRQoL)

- Company's systematic review did not identify any studies reporting utility scores relating to LSCD
- Company took 2 broad approaches to derive modelled utility values:
  1. De novo SG stated preference exercise using 520 members of public
  2. Burden of disease systematic review. Identified key symptoms that drive overall utility of patients with LSCD: (i) VA, (ii) pain, (iii) burning, (iv) photophobia and (v) disfigurement. Additional literature search for associated disutility values.
- Pain is a probabilistic function of health states.
- Disfigurement assumed present in all states except for patients in stable condition with no SS.

Utilities used in company's model

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

Source: CS Table 48

Company: Adverse events

- Sourced from expert clinical opinion and Holoclar SmPC because study data are incomplete/inconsistent
- Glaucoma is the only AE described in the CS
- Assumed to impact on costs but not HRQoL

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

Source: CS p. 221

Company: Resources and costs

- **Extraction biopsy:** Biopsy, amniotic membrane, bandage, OP appointment, antibiotic & steroid eye drops and artificial tears.
- **Main transplant:** Intervention-specific costs – Holoclar = £80,000 (**list price – see PMB p.11 for confidential PAS price**), KLAL = £1,057, others = £0; surgery (all), amniotic membrane.
- **Health state costs:**
  - *Stable 1-12mo:* Antibiotic & steroid eye drops, artificial tears, autologous serum eye drops, OP appointments. All zero cost for Holoclar except OP appointments (half as many).
  - *Stable post-12mo:* No ongoing treatment required.
  - *Failure:* No cost (first 12 months post-transplant failure allocated same resource use as BSC)
  - *BSC:* OP appointments, antibiotic & steroid eye drops, artificial tears, flare-up treatments (autologous serum eye drops & oral antibiotics)
  - *Keratoplasty:* Keratoplasty product, major eye procedure, OP appointments, antibiotic & steroid eye drops, artificial tears.

Company base case with PAS

Unilateral	QALYs	Costs	ICER (full option set)	ICER (excluding CLAU)
CLAU	12.64	£[redacted]	Dominating	N/A
Holoclar	12.09	£[redacted]	Dominated	£7,185 (vs lr-CLAL)
KLAL	9.8	£[redacted]	Dominated	Ext dom.
Lr-CLAL	9.73	£[redacted]	Dominated	-
BSC	7.18	£[redacted]	Dominated	Dominated

Bilateral	QALYs	Costs	ICER (full option set)	ICER (excluding CLAU)
CLAU	10.08	£[redacted]	Dominating	N/A
Holoclar	9.25	£[redacted]	Dominated	£12,438 (vs lr-CLAL)
KLAL	6.56	£[redacted]	Dominated	Ext dom.
Lr-CLAL	6.36	£[redacted]	Dominated	-
BSC	2.44	£[redacted]	Dominated	Dominated

Source: CS appendix 9, tables 1 and 8

Company sensitivity analyses with PAS

Scenario	ICER for Holoclar versus next best comparator	
	Full option set	Excluding CLAU
Unilateral DSA		
Base case	Dominated*	£7,185 (vs Ir-CLAL)
1. Discount rates=3.5%	Dominated*	£21,182 (vs Ir-CLAL)
2. No disfigurement utility decrement	Dominated*	£35,076 (vs Ir-CLAL)
3. 1+2 plus 4 flares per year in BSC	Dominated*	£25,164 (vs Ir-CLAL)
4. 2+ alternative comp. success rates	£488,615 (vs CLAU)	£9,138 (vs KLAL)
5. Alternative rates + 22yr time horizon	£167,223 (vs CLAU)	£29,369 (vs. KLAL)
Bilateral DSA		
Base case	Dominated*	£12,438 (vs Ir-CLAL)
1. 3.5% discount rates	Dominated*	£34,817 (vs Ir-CLAL)
2. No disfigurement utility decrement	Dominated*	£31,850 (vs Ir-CLAL)
3. 1+2plus 4 flares per year in BSC	Dominated*	£39,595 (vs KLAL)
4. 2+ alternative comp. success rates	£485,692 (vs CLAU)	£19,085 (vs KLAL)
5. Alternative rates + 22yr time horizon	£255,563 (vs CLAU)	£27,898 (vs KLAL)
* Dominated by CLAU		

PSA indicates probability CLAU being most cost effective is 1.0

Source: CS Tables 58-67

ERG critique (1)

Model structure

- For CLAU and Holoclar company assume patients with successful transplants at 12 months have successful transplants for life. No evidence to support this and assumption cannot be modified.

Discount rates

- Company used a discount rate of 1.5%. ERG considered this to be inappropriate and used 3.5% in exploratory analyses

Clinical effectiveness

- No data to support Holoclar to treat both eyes
- Issues with data quality noted in clinical section
- Company state inappropriate to pool data because of parameter heterogeneity, yet data in model are pooled
- Weak comparator evidence needs to be taken into account

ERG critique (2)

Health Related Quality of Life

- No HRQoL data available for Holoclar or comparators
- Utilities implausibly low e.g. most are below 0.36. More appropriate values should be chosen for 2 key drivers of HRQoL:
  - VA utility values. ERG used alternative source with more plausible maximum value of 0.840 (rather than 0.706)
  - Disfigurement. Decrement of 0.318 for disfigurement in any eye if no successful keratoplasty, applied equally regardless of extent of disfigurement. ERG used alternative source with more plausible value (0.140 decrement using cataracts as proxy).

Resources and costs

- 2 key areas have significant impact on incremental costs:
  1. Autologous serum eye drops post-op. Used for comparators but for Holoclar only used <3 months. Unlikely that surgeon using them for CLAU, Lr-CLAL or KLAL will not use them for Holoclar.
  2. Autologous serum eye drops for flare-up. Variable clinical practice and biggest driver of costs. Should have 2 scenarios (treatment with and without use for flare-ups).

ERG critique (3)

Company's 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." Only 1 patient and may not be as effective as in unilateral setting.
- 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 parameter, eye drops account for substantial proportion of BSC costs
- Implausible no 2nd procedure for unilateral LSCD after Lr-CLAL failure
- Models do not include failure rates >12 months after successful transplant.
- Models not fully probabilistic.

ERG exploratory analysis (1) – Unilateral with PAS

Scenario for Holoclar vs treatment Source: ERG tables 34, 35, 36	vs Lr-CLAL	vs KLAL	vs BSC	vs CLAU
A. Company base case	**£7,185***	**£2,255**	**DomT**	DOMINATED
1. Use of Brown 2003 VA utility values	£7,576	£2,367	DomT	
2. ERG preferred decrement for disfigurement	£12,960	£4,107	DomT	
B. ERG preferred utility scenario (1+2)	**£14,291***	**£4,494**	**DomT**	
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	DomT	
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***	-	-	-

"DomT": Holocar dominant (cheaper and more effective than comparator)
"DOMINATED": Holoclar dominated (more expensive & less effective than comparator)

ERG exploratory analysis (2) – Bilateral with PAS

Note: Scenarios vs CLAU not presented by ERG

Scenario for Holoclar vs treatment Source: ERG tables 37, 38, 39	**vs Lr-CLAL**	**vs KLAL**	**vs BSC**
A. Company base case	**£12,438***	**£6,533**	**Dominant**
1. Use of Brown 2003 VA utility values	£13,916	£7,512	Dominant
2. ERG preferred decrement for disfigurement	£18,890	£10,762	Dominant
B. ERG preferred utility scenario (1+2)	**£22,524***	**£13,702**	**Dominant**
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**

"Dominant": Holocar dominant (cheaper and more effective than comparator)

Innovation (1) Company

- Holoclar advantages over comparator include:
  - no immunological rejection (avoids immunosuppression)
  - less donor tissue
  - can treat both eyes and possibility of retreatment
  - bridge to successful keratoplasty for some. Can further improve VA
- Somatic stem cells from patient allows for immediate therapeutic application (advantage vs embryonic)
- 1st stem-cell and living cell-based treatment to receive European MA. Company: this is “one of the most significant milestones achieved by the EMA in the last 20 years” (1st approved stem cell medicine)
- Meets unmet need, rare and debilitating orphan condition
- Won award for innovation and research – UK Prix Galien Orphan Product award

Innovation (2) NICE policy regenerative medicine

- NICE and University of York: investigated fitness for purpose of appraisal process for these treatments because can be (i) expensive per patient (ii) weak evidence base, but (iii) potential for substantial health gains
- NICE Regenerative Medicines and Cell Therapy report (2016) summarised:
  - NICE appraisal methods and decision framework applicable to regenerative medicines and cell therapies
  - Quantifying and presenting clinical outcome and decision uncertainty key
  - Where high uncertainty/high potential benefits, need innovative payment methods to manage/share risk and maximise patient access while evidence immature
  - Discount rate for costs/benefits had very significant impact

Potential equality issues

Company:

- ‘no’ creates equality issue for those injured in armed forces
- more likely to have other life changing injuries vs general population with same condition

ERG:

- This is not an equality or equity issue.

Key issues

- All treatments including Holoclar are dominated by CLAU (Holoclar less effective and more costly than CLAU)
- Effectiveness assumptions based on weak evidence (case series data)
- Bilateral effectiveness data available for only 1 patient
- Have the company used appropriate sources for utilities for this condition?
- Discount rate - 1.5% or 3.5%?
- Assumptions about autologous serum eye drops used for flare-ups and post-operatively
- Would patients be offered a second procedure after failure of CLAL?
- Are the company's assumptions about failure rates plausible?
- Innovation: Holoclar won UK Prix Galien Orphan Product award for innovation in Regenerative medicine – have all the benefits of treatment been quantified?