Slides for projector – CiC redacted

Chair's presentation

Holoclar for treating limbal stem cell deficiency after eye burns

2 Appraisal Committee meeting

Committee C

Lead team: Peter Selby, Judith Wardle, Paul Tappenden

ERG: Liverpool Reviews & Implementation Group

NICE technical team: Irina Voicechovskaja, Alexandra Filby, Frances Sutcliffe

Company: Chiesi Farmaceutici

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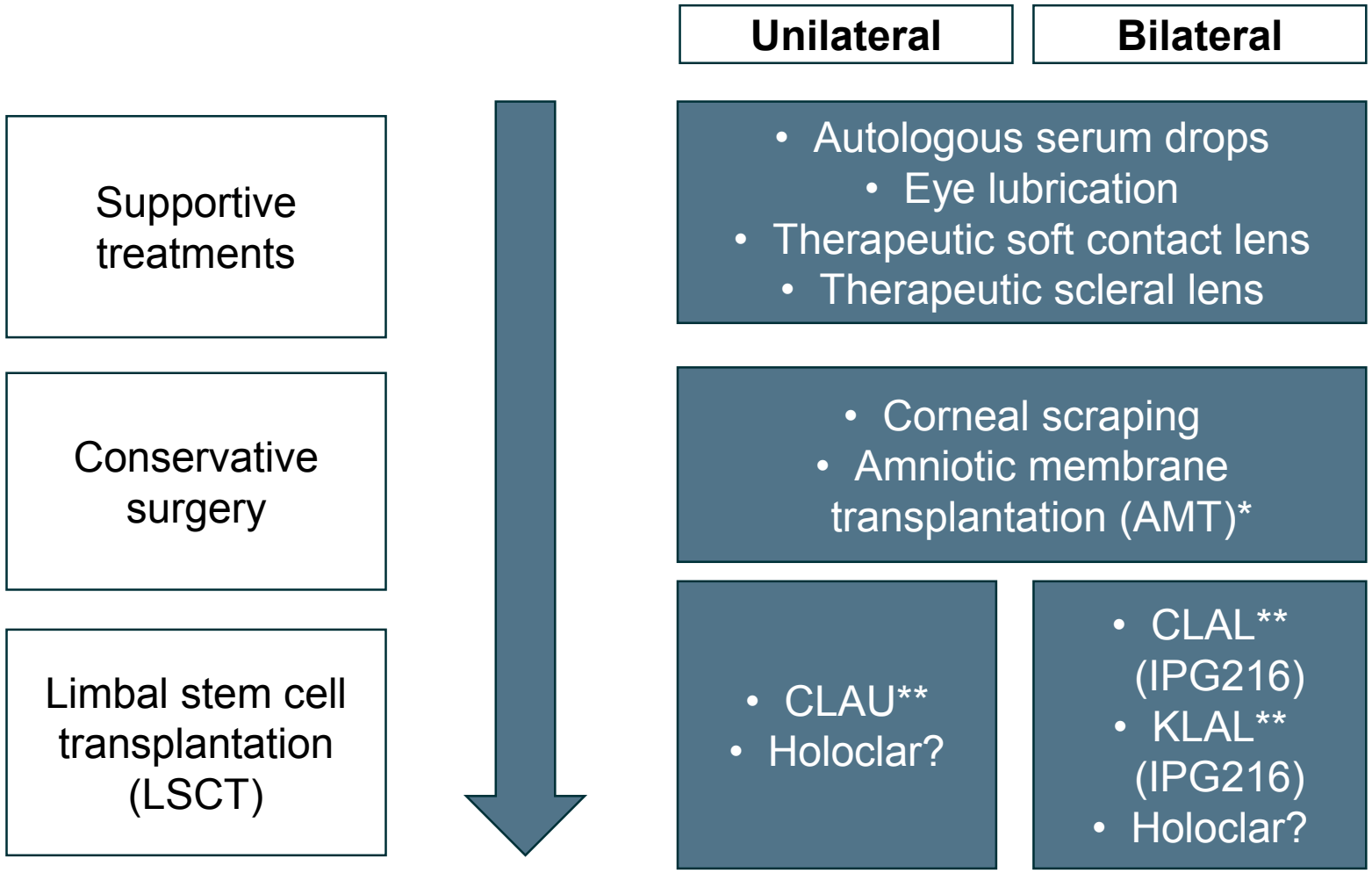
Definitions

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

Holoclar, Chiesi Farmaceutici

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 & dose	Implant administered into eye.

Treatment pathway



*AMT can also be used in combination with LSCT

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

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

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:

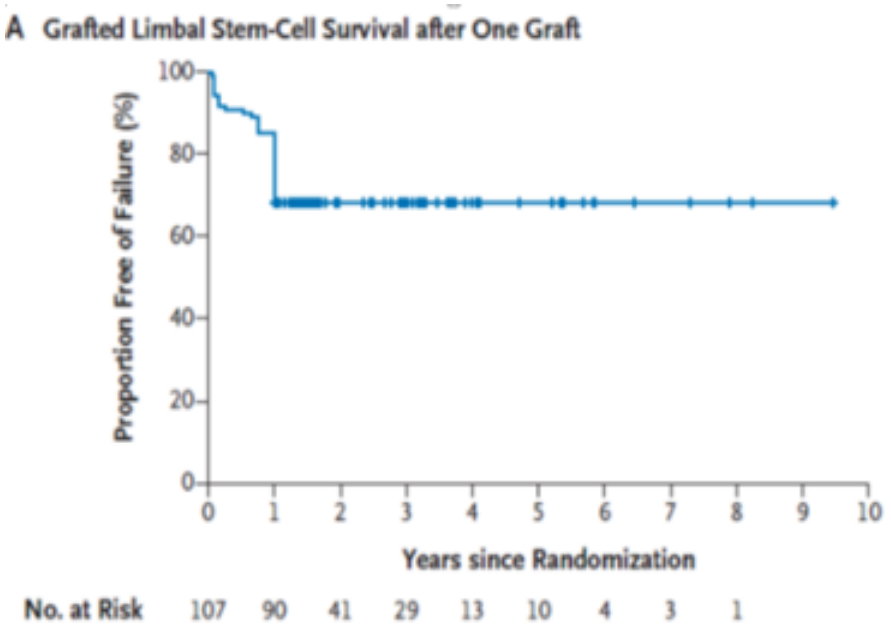
Table: HLSTM01 LSCD symptoms pre and 12 months post surgery

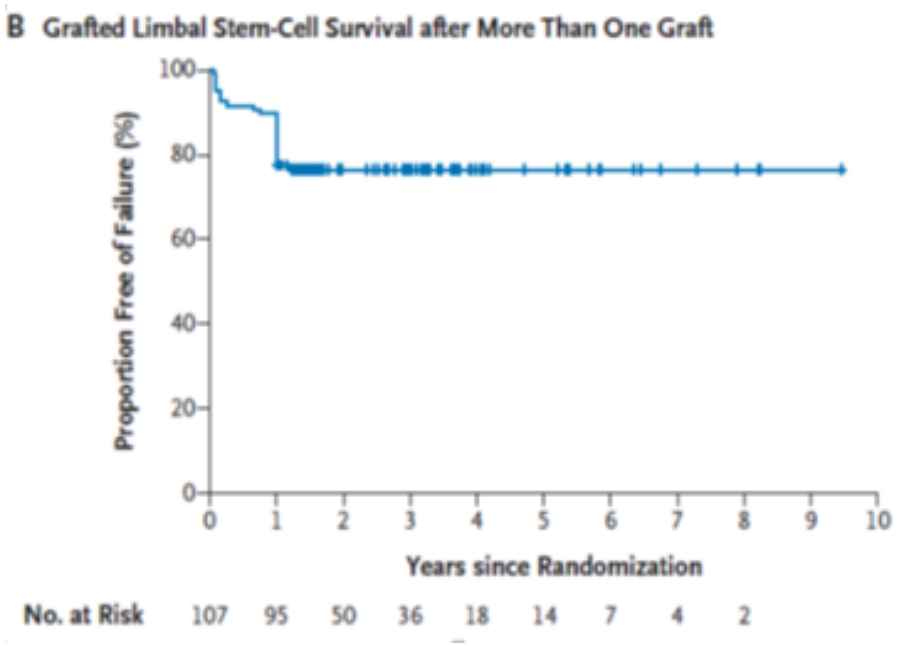
	Pre-surgical assessment n (%)	12 months post-surgery n (%)
Any symptoms	40 (38.5)	12 (11.5)
Pain	7 (6.7)	0(0)*^
Burning	30 (28.8)	7 (6.7)
Photophobia	35 (33.7)	8 (7.7)

* Based on 97 patients
^ Corrected after the second committee meeting

Source: ERG report, p.46

Grafted limbal stem cell survival





Source: CS figure 12. Rama et al. long-term outcome for patients receiving Holoclar

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

Comparator outcomes: Transplant success (ocular surface stability)

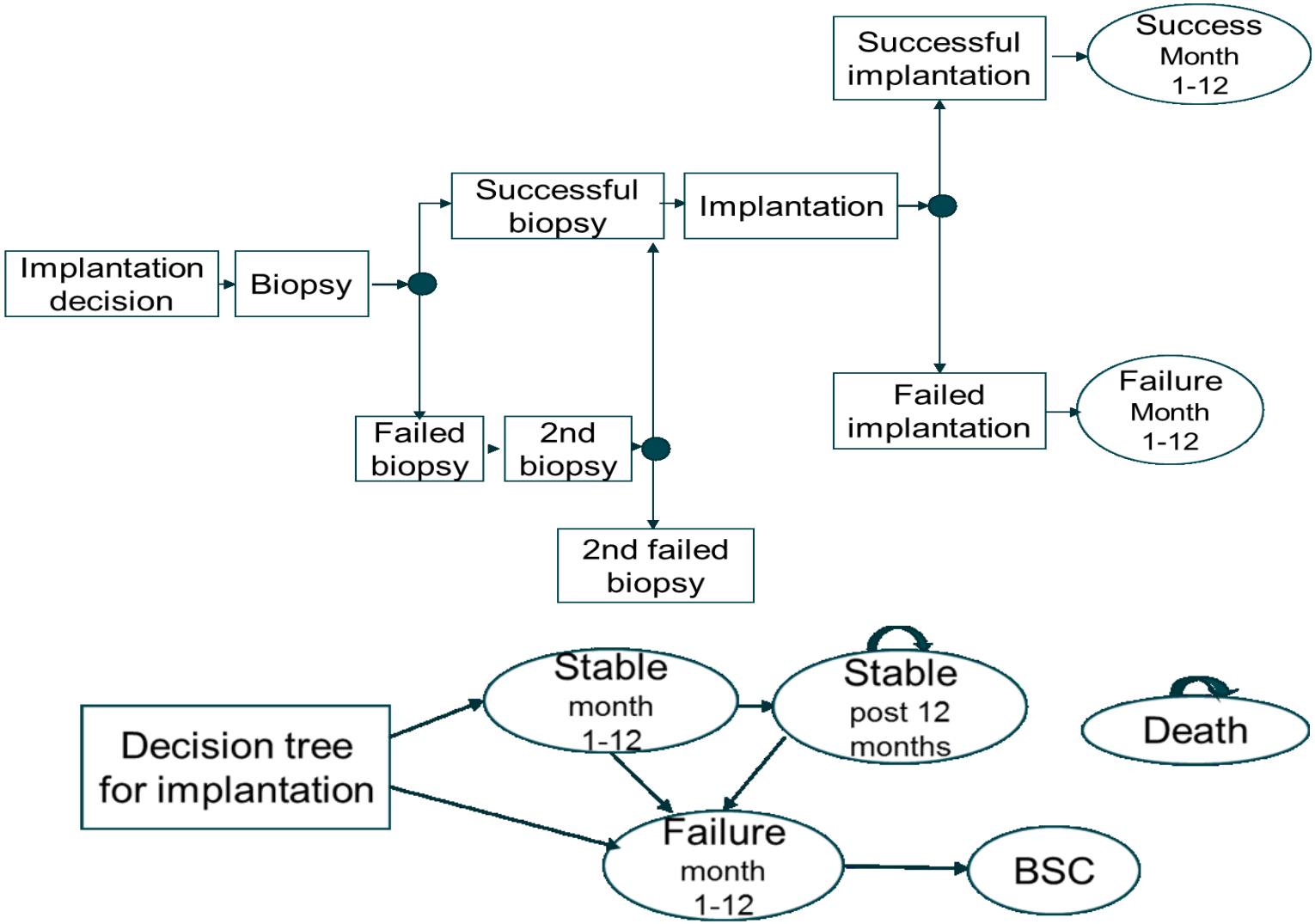
CLAU

- 11 studies, 5 exclusively in ocular burns, and 4 reported success. All unilateral. Success 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

Decision tree and company's model: Unilateral LSCD



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

Source: CS Figures 14 and 15

Key parameters

- Transplant success: restoration of stable cornea with little/no defects or blood vessels in cornea. The company assumed that if transplantation is successful at 12 months then the treatment cures LSCD (for Holoclar and CLAU)
  - Holoclar – from HLSTM01 study
  - Comparators – pooled from literature
- Time horizon - lifetime (50 years)

Parameter	Company	Committee preferred
Discount rate	1.5%	Committee agreed that this was not an exception to the NICE reference case of 3.5%
HRQOL	Czoski-Murray 2009	Brown 2003 (higher VA utilities)
HRQOL disfigurement	Decrement 0.318	Decrement 0.140
Use of autologous serum eye drops	Post-operative use – except after Holoclar	Post-operative use – except after Holoclar

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**

- Modelled utility values were derived form:
  - De novo SG stated preference exercise using 520 members of public
  - Systematic literature review

Source: CS Table 48 *Czoski Murray with Finger adjustment

ERG utility comparison

- 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) (Base case)	Brown (2003)
Highest utility value health state in economic models (unilateral, good prior vision and successful transplant and keratoplasty)	0.706	0.861
Lowest utility value in economic models (bilateral, poor prior vision and unsuccessful transplant with stromal scarring)	0.04	0.285

Source: ERG report p. 81

Company base case with PAS

1.5% discount rate

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 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**	**Dom'ing**	D
1. Use of Brown 2003 VA utility values	£7,576	£2,367	Dom'ing	O
2. ERG preferred decrement for disfigurement	£12,960	£4,107	Dom'ing	M
B. ERG preferred utility scenario (1+2)	**£14,291**	**£4,494**	**Dom'ing**	I
3. 3.5% discount rate	£21,182	£15,245	£3,563	N
C. ERG preferred utility +3.5% discount (1-3)	**£42,139**	**£30,415**	**£6,948**	A
4. Holoclar post-op autologous serum eye drops	£8,129	£3,239	Dom'ing	T
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**	E
5. Eye drops not used flare-ups	£23,328	£16,766	£12,467	D
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***	-	-	-

"Dom'ing": 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)

ACD: preliminary recommendation

- Holoclar is recommended as an option in people with moderate to severe limbal stem cell deficiency … after eye burns, only if:
  - only 1 eye is treated and
  - they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft when 1 eye is affected, or
  - they have already had a conjunctival limbal allograft when both eyes are affected and
  - the company provides it with the discount agreed in the patient access scheme.

Committee's considerations

Issue	Committee's conclusion		
Model structure	Appropriate		
Utility values	Company's maximum utility of 0.706 - implausibly low, ERG's maximum value of 0.861 more plausible		
Decrement for disfigurement	More appropriate decrement of 0.140 (rather than the company's assumption of 0.318), using cataracts as a proxy		
Discount rate	LSCD was very different from the fatal and near-fatal conditions implied by the methods guide therefore 3.5% discount rate should have been used		
Use of eye drops	Agreed that eye drops after treatment were more necessary for the comparators than for Holoclar		
ICERs (with committee's preferred assumptions)	**Holoclar versus**	**1 eye model**	**2 eye model**
	CLAU	CLAU dominates	N/A
	Lr-CLAL	£42,139	£63,047
	KLAL	£30,415	£69,455
	BSC	£6,948	£12,669

ACD consultation responses

- Consultee comments from:
  - Chiesi Farmaceutici
  - Royal College of Ophthalmologists (RCO)
  - Alex Shortt – clinical expert

ACD consultation responses - company

Studies not taken into account in the ACD

- Not all evidence was taken into account (Rama 2001, Rama 2010, Marchini 2012, Pellegrini 2013) in the ACD. Particularly:
  - Rama 2010 - long-term follow-up data for 112 patients treated with Holoclar. Where Holoclar is unsuccessful, all treatment failures occur within the first year and all successfully treated eyes remain stable over time up to 10 years (mean follow-up 2.91 ±1.99 years).
  - Pellegrini 2013 - long-term follow-up data for 152 patients, including data up to 14.5 years (mean follow-up 8.4 ± 2.5 years; range: 5.1–14.5 years).

⊙ *ACD: The committee accepted the assumption about long-term success in the model, but agreed that this was subject to a high level of uncertainty that could increase the ICER*

ACD consultation responses – company
Discount rate

- There is a very good rationale and evidence (Rama 2010, Pellegrini 2013) that include large numbers of patients from the HLSTM01 and HLSTM02 studies, showing that all Holoclar treatments successful at 12 months will continue to be successful over the lifetime of the patient.
- The higher utility decrement suggests LSCD is severely debilitating
- It would be very difficult for any new technology to have 30 year follow-up data available at the time of Marketing Authorisation.

- *ACD: It is rarely considered appropriate to change the discount rate*
- *ACD: LSCD is very different from the fatal and near-fatal conditions implied by the methods guide*
- *NICE methods guide: non-reference-case discount rate may be considered '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).'*

ACD consultation responses - company

Utility decrement for disfigurement

- Unclear in the ACD and the ERG's report why the ERG have proposed cataract as a proxy for LSCD to inform the value of the utility decrement for disfigurement
- Company believes 0.318 decrement is more reasonable than 0.140 (preferred utility) for several reasons (appearance difference, difference in demographic population in which cataracts occurs, clinical experts agree it is high)
- Cataract is not an acceptable or reasonable proxy for LSCD in relation to disfigurement.

- *ACD: The committee concluded that uncertainty remained in the utility values, but the ERG values were a far more realistic reflection of the impact on QOL*
- *ACD: The committee agreed that it was difficult to resolve the inconsistency in the relative importance of disfigurement.*
- *ACD: [the decrement] was over 100-times higher than the utility decrement applied to people experiencing any pain, burning or photophobia*
- *NICE methods guide: the EQ-5D is the preferred measure of health-related quality of life in adults. Health-related quality of life … should be measured directly by patients [this] should be based on a valuation of public preferences from a representative sample of the UK population*

ACD consultation responses - company

Sensitivity analyses

- Sensitivity analysis was submitted in response to the ACD stating it would be useful to explore a range of different success rates.
- Discount rates - 3.5%; a utility value of 0.840 as the base case for visual acuity and a utility decrement of 0.140 for disfigurement.
- The company altered the probability of initial transplant success and long-term probability of transplant failure for comparators

⊙ *ACD: it would have been more useful to explore a range of different success rates (between 50% and 80%) because there was no comparative evidence for Holoclar and the clinical experts considered the comparator success rates to be overestimated. The committee concluded that there was a substantial level of uncertainty in the clinical-effectiveness assumptions in the company's model.*

ACD consultation responses - company

Sensitivity analyses

Probability of Transplant Success	Annual Hazard of Transplant Failure	CLAU	Ir-CLAL	KLAL
		ICER (Holoclar relative to alternative	ICER (Holoclar relative to alternative	ICER (Holoclar relative to alternative
1	0	dominated	dominated	dominated
0.9	0	dominated	dominated	dominated
0.8	0	dominated	dominated	dominated
0.7	0	£ 464,860	£ 456,556	dominated
0.6	0	£ 158,564	£ 155,377	dominated
0.5	0	£ 85,039	£ 83,080	dominated
1	0.1	£ 38,395	£ 37,098	£ 506,923
0.9	0.1	£ 32,972	£ 31,785	£ 236,590
0.8	0.1	£ 28,328	£ 27,236	£ 140,331
0.7	0.1	£ 24,307	£ 23,297	£ 91,403
0.6	0.1	£ 20,792	£ 19,854	£ 62,031
0.5	0.1	£ 17,692	£ 16,817	£ 42,592
1	0.2	£ 17,829	£ 16,890	£ 45,625
0.9	0.2	£ 16,360	£ 15,459	£ 37,044
0.8	0.2	£ 14,984	£ 14,118	£ 29,960
0.7	0.2	£ 13,690	£ 12,857	£ 24,024
0.6	0.2	£ 12,472	£ 11,670	£ 18,989
0.5	0.2	£ 11,323	£ 10,551	£ 14,671
1	0.3	£ 12,341	£ 11,499	£ 18,554
0.9	0.3	£ 11,650	£ 10,831	£ 15,878
0.8	0.3	£ 10,984	£ 10,188	£ 13,449
0.7	0.3	£ 10,343	£ 9,568	£ 11,235
0.6	0.3	£ 9,725	£ 8,970	£ 9,212
0.5	0.3	£ 9,129	£ 8,394	£ 7,356
1	0.4	£ 9,883	£ 9,086	£ 9,605
0.9	0.4	£ 9,498	£ 8,719	£ 8,383
0.8	0.4	£ 9,124	£ 8,361	£ 7,233
0.7	0.4	£ 8,759	£ 8,011	£ 6,148
0.6	0.4	£ 8,403	£ 7,671	£ 5,124
0.5	0.4	£ 8,055	£ 7,339	£ 4,155
1	0.5	£ 8,532	£ 7,761	£ 5,350
0.9	0.5	£ 8,305	£ 7,548	£ 4,718
0.8	0.5	£ 8,082	£ 7,338	£ 4,112
0.7	0.5	£ 7,864	£ 7,133	£ 3,529
0.6	0.5	£ 7,649	£ 6,931	£ 2,969
0.5	0.5	£ 7,438	£ 6,733	£ 2,430

ACD consultation responses – company & clinical expert

Recommendations do not take current management of LSCD into account

- CLAU
  - Due to the risks (3-5% risk to other eye) and uncertain outcome (50% failure rate) patients often refuse to undergo CLAU
- Lr-CLAL:
  - there are difficulties with finding a donor (such as risk to donor's eye),
  - treatment fails in 5 years
  - some patients are contraindicated (due to immunosuppresants)
- For these reasons, some ophthalmology centres do not offer CLAU or lr-CLAU
- The recommendations do not take into account patients who refuse CLAU, cannot identify a donor, are contraindicated or are being treated in centres that do not offer the procedure
- The implicit outcome is that these patients would not receive Holoclar and be managed with BSC which is the least cost-effective option

ACD consultation responses - company
Amended recommendation wording

- Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells) is recommended as an option in people with moderate to severe limbal stem cell deficiency … after eye burns, only if:
  - only 1 eye is treated and
  - they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft *or physician judgement is that these procedures are unsuitable* when 1 eye is affected, or
  - they have already had a conjunctival limbal allograft *or physician judgement is that this procedure is unsuitable* when both eyes are affected and
  - the company provides it with the discount agreed in the patient access scheme.

ACD consultation responses

Guidance review date

- Results of on-going, prospective open label, uncontrolled interventional phase IV study (HLSTM03/HOLOCORE) in 65 patients will be available in 2021
- The company proposes to review the guidance in 4 years not 3 years, when the additional data has been collected.

ACD consultation responses - RCO

- The RCO is not concerned about the culture, transportation and clinical outcomes of Holoclar because it was approved by the EMA based on a very thorough assessment of their system and data provided by the company
- The RCO supports Holoclar even though it is an expensive treatment
- The RCO believes that based on the data from multi-centre EU wide prospective clinical trial and EU registry, the EMA will decide in terms of a full license.

Key issues for consideration

- Were the long-term studies adequately taken into account?
- Should the discount rate of 1.5% be applied?
- What decrement for disfigurement would be the most plausible?
- Do recommendations take current management of LSCD into account adequately?