NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Chiesi Ltd (company)
   - Royal College of Ophthalmologists

3. **Comments on the Appraisal Consultation Document from experts:**
   - Mr Alex Shortt – clinical expert, nominated by Chiesi Ltd

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Holoclar for treating limbal stem cell deficiency after eye burns

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Chiesi</td><td>
Has all of the relevant evidence been taken into account?
It is stated in the ACD that the evidence for the clinical effectiveness of Holoclar comes from three clinical studies, and specifically mentions HLSTM01, HLSTM03 and HLSTM04, with HLSTM01 being pivotal. However, this is not all of the relevant clinical evidence that was included in the company submission in relation to this technology appraisal. The additional evidence for Holoclar is described in four published papers, Rama 2001 (1), Rama 2010 (2), Marchini 2012 (3) and Pellegrini 2013 (4).

Two of these papers are particularly pertinent to the ACD, which in several places comments on the lack of long-term data to demonstrate a sustained effect of Holoclar. Rama 2010 presents long-term follow-up data for 112 patients treated with Holoclar and shows that in cases where treatment with Holoclar is unsuccessful, all treatment failures occur within the first year and that all successfully treated eyes remain stable over time with up to 10 years (mean follow-up 2.91 ±1.99 years) of follow-up data presented. Pellegrini 2013 reported additional long-term follow-up data for Holoclar in 152 patients, including data up to 14.5 years (mean follow-up 8.4 ± 2.5 years; range: 5.1–14.5 years).

As previously explained to the Evidence Review Group in response to their clarification requests, there is significant overlap between the patients included in HLSTM01 and HLSTM02 and these two published papers that present their long-term outcomes:

<table>
<tr><td>Study</td><td>Duration of Follow-up</td><td>Total number of Patients</td><td>Patients from HLSTM01</td><td>Patients from HLSTM02</td></tr>
<tr><td>Rama 2010</td><td>10 years</td><td>112</td><td>93</td><td>0</td></tr>
<tr><td>Pellegrini 2013</td><td>14.5 years</td><td>152</td><td colspan="2">133</td></tr>
</table>
</td><td>Comment noted. Section 4.5 of the final appraisal determination (FAD) has been updated to include the four additional papers that the committee considered.</td></tr>
</table>

	This evidence, although contained in the company submission, appears not to have been taken into account in the ACD and clearly demonstrates the favourable long-term and sustained outcomes of patients treated with Holoclar in the HLSTM01 and HLSTM02 studies and would surely address any uncertainty on this point in the ACD.	
Chiesi	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The ACD suggests that the utility values used in the company's model were far lower than any used in previous appraisals for eye treatments and that the main reason for these low values appeared to be the utility decrement of 0.318 applied to patients experiencing disfigurement. Instead the ERG have used a utility decrement of 0.140 taking cataracts as a proxy. The value of the utility decrement for disfigurement used in the company's model was taken from a bespoke standard gamble (SG) stated preference exercise in 520 UK participants who were presented with various clinical scenarios describing moderate to severe limbal stem cell deficiency (LSCD), including an image of a patient's eye with this condition showing the extent of the disfigurement typically present. It is stated in section 5.3.10 of the ERG's Report describing their model validation and face validity check that, *"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.* It is acknowledged in the ACD that the clinical experts present at the Appraisal Committee meeting also agreed that the impact of disfigurement in patients with LSCD can cause a major health burden whereby patients with unilateral LSCD, contrary to conventional wisdom, will even prioritise improvement in disfigurement over improvement in visual acuity as the more important outcome of treatment for LSCD. The same certainly cannot be said of cataract.	Comment noted. The committee has reconsidered utility values and utility decrement for disfigurement and agreed that cataract disutilities were only proxies. The committee's decision that the ERG's utilities were a more realistic reflection of the impact on quality of life has not changed. Section 4.13 of the FAD has been updated.

	It is 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, contrary to the opinion of clinical experts in the condition, including the clinical experts consulted by the ERG. Indeed, it would be difficult to justify the selection of cataract as a proxy for LSCD as the appearance of the eye and the location and extent of the eye disfigurement in the two conditions are entirely different and far more extensive, unsightly and obvious in LSCD. In addition, LSCD and cataract occur in two very different demographic populations. It should also be noted that age has been shown to be a significant factor in the impact of facial disfigurement (5). The mean age at the time of severe chemical corneal injury in the UK is 33.8 years (median 38.5 years, range 10-59 years) (6). In contrast, cataract in the UK is primarily age-related and a condition that occurs in the elderly (7), especially in the advanced stages when opacification of the lens may become noticeable as a potential disfigurement. For these reasons, it is therefore both plausible and likely that these two demographically distinct populations will attribute different values for the utility decrement of any disfigurement associated with these two very different eye conditions, hence cataract is not an acceptable or reasonable proxy for LSCD in relation to disfigurement. Given that the clinical experts referred to by the ERG in their report and the clinical experts at the Appraisal Committee meeting all agree that the value of the utility decrement for disfigurement in LSCD is high, and that the company derived the value used in their model from specific research using typical clinical scenarios and images of LSCD, it is difficult to interpret why the ACD adopts the ERG's proxy cataract approach in this respect. The company therefore believes that the more reasonable interpretation of the evidence is that a utility decrement value of 0.318 is indeed valid for LSCD and therefore is the more appropriate figure to use in the model compared with the 0.140 value proposed as a proxy by the ERG and obtained from a clinically different and less severe condition, i.e. cataract, that occurs in a demographically older population who Gardiner *et al* (5) have shown to be less impacted by disfigurement.	
Chiesi	**Impact on the Cost-Effectiveness of Holoclar** In relation to the discount rate used by the company in its model for future costs and benefits, Chiesi notes that the ACD rejects the 1.5% rate used by the company in favour of the base case of 3.5%. The NICE methods guide states that when appraising treatments that, *"restore people who would otherwise die or have severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)"*, non-reference case rates may be considered.	Comment noted. The committee has accepted the evidence for the probable long-term success of Holoclar. However, it agreed that the 3.5% discount should be applied. Please see section 4.9 of the FAD.

	It is acknowledged in the ACD that the Appraisal Committee agreed that LSCD can be a life-changing and severely debilitating condition and that the clinical experts stated that successfully treating LSCD could also be life-changing. Indeed, the utility decrements identified by the company in a bespoke standard gamble (SG) stated preference exercise in 520 UK participants who were presented with various clinical scenarios describing moderate to severe LSCD would support this. Furthermore, it is acknowledged in the ACD that this SG study suggests some of the utility decrement values obtained for LSCD are lower than those for people in the last 3 months of life having palliative treatment for various cancers, although the ACD appears to dismiss these findings contrary to the opinion of clinical experts who in both the ACD and ERG Report appear to support them. Chiesi believes that a more reasonable interpretation of the whole evidence, including the long-term follow-up data described by Rama (2) and Pellegrini (4), show that both criteria for use of the 1.5% discount rate have indeed been met. Given that it is limbal stem cells that are being transplanted and that the cornea can be expected to regenerate 3-4 times per year, there is a very good rationale and evidence with the 10 year and subsequently the 14.5 year data that include large numbers of patients from the HLSTM01 and HLSTM02 studies, to interpret these data as evidence that, as described in the company submission, all Holoclar treatments that are successful at 12 months will continue to be successful over the lifetime of the patient. Chiesi notes that it would be very difficult and unlikely for any new technology to have 30 year follow-up data available at the time of Marketing Authorisation. Given the mechanism of action of Holoclar, i.e. stem cell therapy, coupled with follow-up data for patients in the HLSTM01 study available for up to 14.5 years, and the extent of the health-related quality of life burden of LSCD and hence life-changing impact of successful treatment, it may indeed be more reasonable to conclude that the discount rate of 1.5% is the more appropriate choice for this technology appraisal. Clearly, both these points will have a significant impact on the calculated ICERs and the conclusions as to the relative cost-effectiveness of Holoclar based upon them, especially in relation to living-related conjunctival-limbal allograft (lr-CLAL) and keratolimbal allograft (KLAL). However, we would request that the Appraisal Committee look again at the evidence to support the utility decrements associated with LSCD and the long-term sustained benefits that are achieved with Holoclar and reconsider the choice of discount rate to apply.	

Chiesi	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The recommendations presented in the ACD fail to take account of several important points in relation to the management of LSCD within the NHS: • It is acknowledged in the ACD that the clinical experts stated 3-5% of patients undergoing CLAU would have permanent serious damage to the donor eye and that the estimated success rate for CLAU in the affected eye was 50%. It is therefore clear that, even in expert hands, 50% patients treated with CLAU will be left with an affected eye unsuccessfully treated and for 3-5% of these, their only previously healthy eye will be left with permanent serious damage as a consequence of the CLAU procedure. It is also acknowledged in the ACD that the clinical experts were not aware of any instances of damage to the donor eye for Holoclar. Given that this is how clinical experts in LSCD will likely also council their patients, a significant number of patients with unilateral LSCD therefore refuse to undergo CLAU due to the combination of an uncertain outcome in the affected eye (50% failure rate) and the risks of permanent serious damage to the unaffected eye (3-5%). The ACD acknowledges that the clinical experts stated that patient refusal to undergo CLAU was often the case. i) It is acknowledged in the ACD that the clinical experts explained finding a source of donor tissue can be problematic. It cannot therefore be assumed that every patient with LSCD has an available and willing (ideally first degree) relative prepared to act as a donor for lr-CLAL. Furthermore, the risk of serious permanent damage to the donor eye is 3-5%, and even if initially successful the procedure will fail within 5 years. After this time the patient at best returns to their status prior to lr-CLAL (although due to the recognised side effects of the associated immunosuppression this should not be assumed) and 3-5% of previously healthy donors have permanent serious damage to their eye. Understandably not all potential donors are willing to accept this risk to their own eye for a benefit to their relative that even if initially successful will not last beyond 5 years. ii) Some patients may be unsuitable to receive lr-CLAL due to contra-indications to the associated immunosuppression that is required for this procedure, which should be continued until the point in time that the graft ultimately fails, i.e. up to 5 years. As described in the company submission, systemic immunosuppression with mycophenolate is the immunosuppressant of choice for lr-CLAL in patients with LSCD(8). However, this cannot be given during pregnancy or to women of child-bearing potential who are not using highly effective contraception. In addition, elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and gastrointestinal haemorrhage and pulmonary oedema (9).	Comment noted. The recommendations (section 1) have been changed after the second appraisal committee meeting.

	iii) For the reasons stated above, some specialist ophthalmology centres do not offer either CLAU or lr-CLAL and these procedures are therefore not available to all patients within the NHS. The ACD acknowledges that one clinical expert stated that they no longer offered CLAU. However, this is not a fully accurate description of what was expressed by the clinical expert who stated that they considered CLAU and lr-CLAL (and KLAL) to be questionable both on clinical and, in the case of lr-CLAL, ethical grounds such that they do not offer any of these procedures and have not for many years. Furthermore, the other clinical expert stated that they had undertaken only 5 CLAU procedures throughout their entire professional career. The recommendations proposed in the ACD do not therefore take account of cases where patients refuse CLAU, and/or an available and willing living-related donor cannot be identified, and/or lr-CLAL is unsuitable and/or patients are being treated in NHS centres where these procedures are not recommended by their treating ophthalmologist. The current recommendations do not provide any explicit guidance for these patients. Indeed, the implicit outcome is that these patients would not receive Holoclar and by default be manged with best supportive care (BSC), which it is agreed is not cost-effective and indeed dominated. By revisiting the UK incidence and prevalence data for moderate to severe LSCD due to chemical or physical burns it is clear that, contrary to the opinion of the ERG, this group of patients is very real within the NHS. The estimated incidence of new cases of severe chemical corneal injury in the UK is 0.02 in 100,000 people (13 new cases per year) with a mean age at the time of injury of 33.8 years (median 38.5 years, range 10-59 years), i.e. encompassing the child-bearing years for women (6). In contrast, the prevalent population believed to match the indication for Holoclar is estimated at 121 patents in the UK (10). Clearly if CLAU and lr-CLAL, which have been available for many years, were able to meet the needs of, were suitable for and accepted by all patients with moderate to severe LSCD due to chemical and physical burns (and their ophthalmologists), the UK prevalence figure would be far closer to the incidence figure. As this is not the case, there are clearly a significant number of patients in the UK who have either been unsuccessfully treated with the current technologies, are unsuitable for the current technologies, not offered the current technologies by their ophthalmologists or are choosing not to be treated with the current technologies due to concerns over risks to their own health and/or that of a relative, and therefore are being managed with the least cost-effective of all options, i.e. BSC. However, all these points could be addressed by modification of the recommendations as follows: iv) 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 (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity) after eye burns, only if: • only 1 eye is treated and	

<table>
<tr>
<td></td>
<td>

they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft <u>or physician judgement is that these procedures are unsuitable</u> when 1 eye is affected, or
they have already had a conjunctival limbal allograft <u>or physician judgement is that this procedure is unsuitable</u> when both eyes are affected and
the company provides it with the discount agreed in the patient access scheme.

It is only with these (or similarly worded) amendments incorporated are the recommendations a sound and suitable basis for guidance to the NHS and thereby ensure that certain groups of patients do not by default, because the recommendations make no provision for them, receive a treatment (i.e. BSC) that has been shown out of all the options considered in this technology appraisal to be the least cost-effective for the NHS.
</td>
<td></td>
</tr>
<tr>
<td>Chiesi</td>
<td>Finally, Chiesi notes the proposal within the ACD to review this guidance three years after its publication. Chiesi would like to make the Appraisal Committee aware that the results of the currently ongoing prospective, multinational, multicentre, open label, uncontrolled interventional phase IV study (HLSTM03/HOLOCORE), which is being conducted in at least 65 patients with moderate to severe LSCD (plus 5 paediatric patients as agreed in the approved Paediatric Investigation Plan) will most likely be available in 2021. Chiesi suggests that any review of this guidance would be more meaningful with these data included and therefore would like to request that the Appraisal Committee considers a review of this guidance take place in four years not three.</td>
<td>Comment noted. The guidance will be updated after 4 years, please see section 7.1 of the FAD.</td>
</tr>
<tr>
<td>Chiesi</td>
<td>Sensitivity Analyses as requested by the Committee
The Appraisal Committee agreed that 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.
Chiesi have conducted these analyses under the preferred scenarios and published in the ACD i.e. discount rates set at 3.5%; a utility value of 0.840 as the base case for visual acuity and a utility decrement of 0.140 for disfigurement.
<table>
<tr><th></th><th>Total Costs</th><th>Total QALYs</th><th>ICER</th><th>Inc Cost</th><th>Inc QALYs</th><th>ICER (Holoclar relative to)</th></tr>
<tr><td>CLAU</td><td>£ 18,651</td><td>14.60</td><td>0</td><td>£ 69,491</td><td>-0.21</td><td>Dominated</td></tr>
<tr><td>lr-CLAL</td><td>£ 55,782</td><td>13.63</td><td>Dominated</td><td>£ 32,360</td><td>0.77</td><td>£ 42,139</td></tr>
<tr><td>KLAL</td><td>£ 65,932</td><td>13.67</td><td>Dominated</td><td>£ 22,210</td><td>0.73</td><td>£ 30,415</td></tr>
<tr><td>BSC</td><td>£ 75,289</td><td>12.55</td><td>Dominated</td><td>£ 12,853</td><td>1.85</td><td>£ 6,948</td></tr>
<tr><td>Holoclar</td><td>£ 88,142</td><td>14.40</td><td>Dominated</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>Comment noted. The committee considered the company’s sensitivity analyses and it has been taken into account. Please see section 4.12 and 4.15.</td>
</tr>
</table>

	Sensitivity analyses were conducted by altering the probability of the relevant values in the 'survival probabilities' sheet in the excel models, such that for each comparator treatment the probability of initial treatment success is varied by 10% from 100% to 50% and the annual probability of failure after initial success is varied from 0% to 50%. All combinations are modelled using the NICE preferred base case scenario and using the expectations for Holoclar as fixed. Long-term survival is modelled by applying a time-invariant constant probability rate to the population with resolved LSCD and who are still alive at the relevant time in the model, i.e. an exponential parameterisation. For example, setting conjunctival limbal autograft (CLAU) to a 90% chance of initial operative success and a 20% annual probability was obtained by setting cells E21 to 0.9 and cells E22 and E23 to 0.8 on 'survival probabilities' sheet and choosing the 'pooled option' in cell C17 on the control sheet. The results are shown in the accompanying excel spreadsheet 'survival rate sensitivity analyses Holoclar v120417.xlsx'. As expected the cost-effectiveness of Holoclar is highly dependent on the success and survival parameters of the comparators. The long-term QALY loss and costs of unresolved LSCD treated by best supportive care mean that the long-term success of resolved LSCD can overcome high initial treatment costs. The results are most sensitive to the value of the annual failure probability rate i.e. the rate at which successful surgery fails over time. The outcomes for CLAU and lr-CLAL are very similar and differ only because of the additional biopsy costs for lr-CLAL. The Holoclar ICER approaches £30k when for the relevant comparator treatment there is a 10% annual failure probability and initial success is at 90% or below. At any annual probability above 10% the Holoclar ICER is below £30k. For KLAL the results differ as more than one attempt may be made where there is treatment failure. As a result the Holoclar ICER falls beneath £30k whenever the annual failure probability rate is 20% and original operative success is 80% or lower. Where annual failure probabilities exceed 20% Holoclar is always cost-effective. For comparison, the individual studies that inform the pooled rate are indicated on the sensitivity analyses using comments. They have been rounded to the nearest reported values, so they do not completely match the actual ICERs that would be obtained using those figures in the model. For additional comparison the opinion of the clinical experts regarding treatment failure rates (not used in pooling) has also been indicated on the spreadsheet for lr-CLAL and KLAL. Note that the range of sensitivity on annual probability rates is not sufficient to include these estimates rates of failure following successful transplant.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Clinical expert nominated by Chiesi	The management of Limbal Stem Cell Deficiency (LSCD) is a complex and dynamic process. Reducing this to a single algorithm is very difficult. That being said, the recommendations presented in the ACD fail to grasp several core concepts which I tried to convey at the committee meeting but would appear to have faile. The proposed algorithm for the management of LSCD	Comment noted. The committee has changed the recommendation after the second appraisal committee meeting to reflect the comments

	within the NHS is unworkable and represents a waste of time for all concerned in this process. As it currently stands, the draft guidance will see no patients being treated with Holoclar on the NHS. My reasons for making this assertion are as follows: • CLAU is not an acceptable choice for the majority of my patients. The panel would appear to have accepted that 3-5% of patients undergoing CLAU would have permanent serious damage to the donor eye and that the estimated success rate for CLAU in the affected eye is approximately 50%. For these reasons CLAU is clearly a less than optimal technique. When I present patients with this data and offer them a limbal stem cell transplant using the CLAU technique they virtually all decline the procedure. I have done 3 of these procedures in the past 4 years despite offering it to approximately 40 patients. The proposed guidance precludes these patients from receiving Holoclar because they choose not to undergo a procedure which they quite rightly perceive to be high risk and low reward. • For related reasons to the above, lr-CLAL is also an unacceptable choice for most patients as well as for their relatives who are required to donate tissue. To assume that every patient requiring treatment for LCSD has a blood relative available and willing to act as a donor for lr-CLAL is completely wrong. It is my experience that the risk of serious permanent damage to the donor eye is 3-5%. For these reasons it is my experience that relatives frequently refuse to donate tissue and patients with LSCD frequently refuse to allow them. The proposed guidance placed patients and their family members in a difficult position of being forced to undergo this procedure in order to subsequently gain access to Holoclar. • Even if the lr-CLAL is successful in the recipient, data from clinical trails show that all of these grafts fail within 5 years unless the recipient is heavily immunosuppressed at great expense and high risk of complications. Several patients have contra-indications to This adds another barrier to patients choosing to undergo lr-CLAL. It is my experience that for these reasons patients choose conservative, supportive management of their LSCD over lr-CLAL. The proposed guidance will place patients in the position of needing to take a risk that they find unacceptable in order to gain access to Holoclar.	received during the ACD consultation. Please see section 1 of the guidance. The committee has accepted the evidence for the probable long-term success of Holoclar. However, it agreed that the 3.5% discount should be applied. Please see section 4.9 of the FAD.

	• Several tertiary corneal centres in the UK do not offer either CLAU or Ir-CLAL and these procedures are therefore not available to all patients within the NHS. For NICE to put a guideline in place which requires surgeons to undertake outdated and ineffective procedures with a low sccess rate seems to me to make little sense and simply increases the cost to the NHS were they to do so. I strongly urge the committee to reconsider their guidance. If published as is, this will adversely affect real patients by forcing them to have procedures which are outdated and ineffective and place them at increased risk by requiring them to take toxic immunosuppression in order to gain access to Holoclar. In real terms this guidance will place unnecessary and unfair barriers to patients receiving a treatment which ultimately would benefit them and save the NHS money over conservative management. Lastly, Holoclar offers long term regeneration of the surface of the eye. The results of Prof Rama's NEJM paper in 2014 show that the effect of the therapy appears to be permanent. The insistence of NICE to use a 3% discount is therefore incorrect and a 1.5% discount is clearly warranted in this situation.	
Royal College of Ophthalmologists	There are 3 main issues related to this NICE technology appraisal on HOLOCLAR, as follows: 1. Technical aspects including culture, transportation and clinical outcomes: the RCOphth believes there are no issues on these aspects as Holoclar was approved by the EMA based on a very thorough assessment of their system and data provided by the manufacturer. Their clinical data is mainly retrospective and for this reason the EMA granted license is conditional pending a multi-centre EU wide prospective clinical trial involving 65 patients, including five children and a EU registry. With the data from both studies the EMA will decide in terms of a full license. But this will take another three to four years. 2. Label indication for the product: again, this is clear and the College does not have any issues. 3. Cost: It is a rather expensive treatment. This is understandable as it is a cell therapy. The company has proposed a discounted rate for the U.K. There is some disquiet regarding the high cost however, it will be the only licensed product available in EU. In summary, this is the first cell therapy approved by the EMA that will be approved at EU member states level widely and as stated above the RCOphth supports it.	Comment noted.

Comments received from commentators

None

Comments received from members of the public

None

Summary of comments received from members of the public

None

CHIESI LIMITED
Manchester Green,
333 Styal Road,
Manchester M22 5LG
Tel: 0161 488 5555
Fax: 0161 488 5566
info.uk@chiesi.com

Stephanie Yates
Project Manager
Technology Appraisals – Committee C
National Institute for Health and Care Excellence

8th May 2017

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 Stephanie,

Re: Company Response to Appraisal Consultation Document

Thank you for the opportunity to comment on the appraisal consultation document (ACD) that was issued on 5th April 2017. In response to the appraisal committee's specific points of interest, Chiesi would like to comment as follows:

Has all of the relevant evidence been taken into account?

It is stated in the ACD that the evidence for the clinical effectiveness of Holoclar comes from three clinical studies, and specifically mentions HLSTM01, HLSTM03 and HLSTM04, with HLSTM01 being pivotal. However, this is not all of the relevant clinical evidence that was included in the company submission in relation to this technology appraisal. The additional evidence for Holoclar is described in four published papers, Rama 2001 (1), Rama 2010 (2), Marchini 2012 (3) and Pellegrini 2013 (4).

Two of these papers are particularly pertinent to the ACD, which in several places comments on the lack of long-term data to demonstrate a sustained effect of Holoclar. Rama 2010 presents long-term follow-up data for 112 patients treated with Holoclar and shows that in cases where treatment with Holoclar is unsuccessful, all treatment failures occur within the first year and that all successfully treated eyes remain stable over time with up to 10 years (mean follow-up 2.91 ±1.99 years) of follow-up data presented. Pellegrini 2013 reported additional long-term follow-up data for Holoclar in 152 patients, including data up to 14.5 years (mean follow-up 8.4 ± 2.5 years; range: 5.1–14.5 years).

As previously explained to the Evidence Review Group in response to their clarification requests, there is significant overlap between the patients included in HLSTM01 and HLSTM02 and these two published papers that present their long-term outcomes:

Study	Duration of Follow-up	Total number of Patients	Patients from HLSTM01	Patients from HLSTM02
Rama 2010	10 years	112	93	0
Pellegrini 2013	14.5 years	152	133	

This evidence, although contained in the company submission, appears not to have been taken into account in the ACD and clearly demonstrates the favourable long-term and sustained outcomes of patients treated with Holoclar in the HLSTM01 and HLSTM02 studies and would surely address any uncertainty on this point in the ACD.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The ACD suggests that the utility values used in the company's model were far lower than any used in previous appraisals for eye treatments and that the main reason for these low values appeared to be the utility decrement of 0.318 applied to patients experiencing disfigurement. Instead the ERG have used a utility decrement of 0.140 taking cataracts as a proxy.

The value of the utility decrement for disfigurement used in the company's model was taken from a bespoke standard gamble (SG) stated preference exercise in 520 UK participants who were presented with various clinical scenarios describing moderate to severe limbal stem cell deficiency (LSCD), including an image of a patient's eye with this condition showing the extent of the disfigurement typically present. It is stated in section 5.3.10 of the ERG's Report describing their model validation and face validity check that, *"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.* It is acknowledged in the ACD that the clinical experts present at the Appraisal Committee meeting also agreed that the impact of disfigurement in patients with LSCD can cause a major health burden whereby patients with unilateral LSCD, contrary to conventional wisdom, will even prioritise improvement in disfigurement over improvement in visual acuity as the more important outcome of treatment for LSCD. The same certainly cannot be said of cataract.

It is 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,

contrary to the opinion of clinical experts in the condition, including the clinical experts consulted by the ERG. Indeed, it would be difficult to justify the selection of cataract as a proxy for LSCD as the appearance of the eye and the location and extent of the eye disfigurement in the two conditions are entirely different and far more extensive, unsightly and obvious in LSCD. In addition, LSCD and cataract occur in two very different demographic populations. It should also be noted that age has been shown to be a significant factor in the impact of facial disfigurement (5). The mean age at the time of severe chemical corneal injury in the UK is 33.8 years (median 38.5 years, range 10-59 years) (6). In contrast, cataract in the UK is primarily age-related and a condition that occurs in the elderly (7), especially in the advanced stages when opacification of the lens may become noticeable as a potential disfigurement. For these reasons, it is therefore both plausible and likely that these two demographically distinct populations will attribute different values for the utility decrement of any disfigurement associated with these two very different eye conditions, hence cataract is not an acceptable or reasonable proxy for LSCD in relation to disfigurement.

Given that the clinical experts referred to by the ERG in their report and the clinical experts at the Appraisal Committee meeting all agree that the value of the utility decrement for disfigurement in LSCD is high, and that the company derived the value used in their model from specific research using typical clinical scenarios and images of LSCD, it is difficult to interpret why the ACD adopts the ERG's proxy cataract approach in this respect. The company therefore believes that the more reasonable interpretation of the evidence is that a utility decrement value of 0.318 is indeed valid for LSCD and therefore is the more appropriate figure to use in the model compared with the 0.140 value proposed as a proxy by the ERG and obtained from a clinically different and less severe condition, i.e. cataract, that occurs in a demographically older population who Gardiner *et al* (5) have shown to be less impacted by disfigurement.

Impact on the Cost-Effectiveness of Holoclar

In relation to the discount rate used by the company in its model for future costs and benefits, Chiesi notes that the ACD rejects the 1.5% rate used by the company in favour of the base case of 3.5%. The NICE methods guide states that when appraising treatments that, *"restore people who would otherwise die or have severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)"*, non-reference case rates may be considered.

It is acknowledged in the ACD that the Appraisal Committee agreed that LSCD can be a life-changing and severely debilitating condition and that the clinical experts stated that successfully treating LSCD could also be life-changing. Indeed, the utility decrements identified by the company in a bespoke standard gamble (SG) stated preference exercise in 520 UK participants who were presented with various clinical scenarios describing moderate to severe LSCD would support this. Furthermore, it is acknowledged in the ACD that this SG study suggests some of the utility decrement

values obtained for LSCD are lower than those for people in the last 3 months of life having palliative treatment for various cancers, although the ACD appears to dismiss these findings contrary to the opinion of clinical experts who in both the ACD and ERG Report appear to support them.

Chiesi believes that a more reasonable interpretation of the whole evidence, including the long-term follow-up data described by Rama (2) and Pellegrini (4), show that both criteria for use of the 1.5% discount rate have indeed been met. Given that it is limbal stem cells that are being transplanted and that the cornea can be expected to regenerate 3-4 times per year, there is a very good rationale and evidence with the 10 year and subsequently the 14.5 year data that include large numbers of patients from the HLSTM01 and HLSTM02 studies, to interpret these data as evidence that, as described in the company submission, all Holoclar treatments that are successful at 12 months will continue to be successful over the lifetime of the patient.

Chiesi notes that it would be very difficult and unlikely for any new technology to have 30 year follow-up data available at the time of Marketing Authorisation. Given the mechanism of action of Holoclar, i.e. stem cell therapy, coupled with follow-up data for patients in the HLSTM01 study available for up to 14.5 years, and the extent of the health-related quality of life burden of LSCD and hence life-changing impact of successful treatment, it may indeed be more reasonable to conclude that the discount rate of 1.5% is the more appropriate choice for this technology appraisal.

Clearly, both these points will have a significant impact on the calculated ICERs and the conclusions as to the relative cost-effectiveness of Holoclar based upon them, especially in relation to living-related conjunctival-limbal allograft (lr-CLAL) and keratolimbal allograft (KLAL). However, we would request that the Appraisal Committee look again at the evidence to support the utility decrements associated with LSCD and the long-term sustained benefits that are achieved with Holoclar and reconsider the choice of discount rate to apply.

Sensitivity Analyses as requested by the Committee

The Appraisal Committee agreed that 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.

Chiesi have conducted these analyses under the preferred scenarios and published in the ACD i.e. discount rates set at 3.5%; a utility value of 0.840 as the base case for visual acuity and a utility decrement of 0.140 for disfigurement.

	Total Costs	Total QALYs	ICER	Inc Cost	Inc QALYs	ICER (Holoclar relative to)
CLAU	£ 18,651	14.60	0	£ 69,491	-0.21	Dominated

lr-CLAL	£ 55,782	13.63	Dominated	£ 32,360	0.77	£ 42,139
KLAL	£ 65,932	13.67	Dominated	£ 22,210	0.73	£ 30,415
BSC	£ 75,289	12.55	Dominated	£ 12,853	1.85	£ 6,948
Holoclar	£ 88,142	14.40	Dominated			

Sensitivity analyses were conducted by altering the probability of the relevant values in the 'survival probabilities' sheet in the excel models, such that for each comparator treatment the probability of initial treatment success is varied by 10% from 100% to 50% and the annual probability of failure after initial success is varied from 0% to 50%. All combinations are modelled using the NICE preferred base case scenario and using the expectations for Holoclar as fixed.

Long-term survival is modelled by applying a time-invariant constant probability rate to the population with resolved LSCD and who are still alive at the relevant time in the model, i.e. an exponential parameterisation. For example, setting conjunctival limbal autograft (CLAU) to a 90% chance of initial operative success and a 20% annual probability was obtained by setting cells E21 to 0.9 and cells E22 and E23 to 0.8 on 'survival probabilities' sheet and choosing the 'pooled option' in cell C17 on the control sheet. The results are shown in the accompanying excel spreadsheet 'survival rate sensitivity analyses Holoclar v120417.xlsx'.

As expected the cost-effectiveness of Holoclar is highly dependent on the success and survival parameters of the comparators. The long-term QALY loss and costs of unresolved LSCD treated by best supportive care mean that the long-term success of resolved LSCD can overcome high initial treatment costs. The results are most sensitive to the value of the annual failure probability rate i.e. the rate at which successful surgery fails over time. The outcomes for CLAU and lr-CLAL are very similar and differ only because of the additional biopsy costs for lr-CLAL. The Holoclar ICER approaches £30k when for the relevant comparator treatment there is a 10% annual failure probability and initial success is at 90% or below. At any annual probability above 10% the Holoclar ICER is below £30k. For KLAL the results differ as more than one attempt may be made where there is treatment failure. As a result the Holoclar ICER falls beneath £30k whenever the annual failure probability rate is 20% and original operative success is 80% or lower. Where annual failure probabilities exceed 20% Holoclar is always cost-effective.

For comparison, the individual studies that inform the pooled rate are indicated on the sensitivity analyses using comments. They have been rounded to the nearest reported values, so they do not completely match the actual ICERs that would be obtained using those figures in the model. For additional comparison the opinion of the clinical experts regarding treatment failure rates (not used in pooling) has also been indicated on the spreadsheet for lr-CLAL and KLAL. Note that the range of sensitivity on annual probability rates is not sufficient to include these estimates rates of failure following successful transplant.

Probability of Transplant Success	Annual Probability of Transplant Failure	CLAU					Ir-CLAL					KLAL				
		Expected Costs	Expected QALYs	Incremental costs of Holoclar	Incremental QALYs of Holoclar	ICER (Holoclar relative to alternative	Expected Costs	Expected QALYs	Incremental costs of Holoclar	Incremental QALYs of Holoclar	ICER (Holoclar relative to alternative	Expected Costs	Expected QALYs	Incremental costs of Holoclar	Incremental QALYs of Holoclar	ICER (Holoclar relative to alternative
1	0	£ 9,551	14.86	£ 78,591	-0.47	dominated	£ 10,612	14.86	£ 77,530	-0.47	dominated	£ 10,908	14.86	£ 77,234	-0.47	dominated
0.9	0	£ 16,441	14.67	£ 71,701	-0.27	dominated	£ 17,493	14.67	£ 70,648	-0.27	dominated	£ 11,824	14.85	£ 76,317	-0.45	dominated
0.8	0	£ 23,331	14.47	£ 64,811	-0.07	dominated	£ 24,375	14.47	£ 63,767	-0.07	dominated	£ 13,262	14.83	£ 74,879	-0.43	dominated
0.7	0	£ 30,221	14.27	£ 57,921	0.12	£ 464,860	£ 31,256	14.27	£ 56,886	0.12	£ 456,556	£ 15,594	14.78	£ 72,548	-0.38	dominated
0.6	0	£ 37,111	14.08	£ 51,031	0.32	£ 158,564	£ 38,137	14.08	£ 50,005	0.32	£ 155,377	£ 19,189	14.70	£ 68,953	-0.30	dominated
0.5	0	£ 44,001	13.88	£ 44,140	0.52	£ 85,039	£ 45,018	13.88	£ 43,124	0.52	£ 83,080	£ 24,420	14.57	£ 63,722	-0.17	dominated
1	0.1	£ 56,724	13.58	£ 31,418	0.82	£ 38,395	£ 57,785	13.58	£ 30,357	0.82	£ 37,098	£ 40,537	14.30	£ 47,604	0.09	£ 506,923
0.9	0.1	£ 58,897	13.51	£ 29,245	0.89	£ 32,972	£ 59,949	13.51	£ 28,193	0.89	£ 31,785	£ 43,759	14.21	£ 44,383	0.19	£ 236,590
0.8	0.1	£ 61,069	13.44	£ 27,072	0.96	£ 28,328	£ 62,113	13.44	£ 26,029	0.96	£ 27,236	£ 47,297	14.11	£ 40,845	0.29	£ 140,331
0.7	0.1	£ 63,242	13.37	£ 24,900	1.02	£ 24,307	£ 64,277	13.37	£ 23,865	1.02	£ 23,297	£ 51,160	13.99	£ 36,981	0.40	£ 91,403
0.6	0.1	£ 65,415	13.30	£ 22,727	1.09	£ 20,792	£ 66,441	13.30	£ 21,701	1.09	£ 19,854	£ 55,359	13.87	£ 32,783	0.53	£ 62,031
0.5	0.1	£ 67,588	13.24	£ 20,554	1.16	£ 17,692	£ 68,605	13.24	£ 19,537	1.16	£ 16,817	£ 59,903	13.73	£ 28,239	0.66	£ 42,592
1	0.2	£ 67,991	13.27	£ 20,151	1.13	£ 17,829	£ 69,052	13.27	£ 19,089	1.13	£ 16,890	£ 61,029	13.80	£ 27,113	0.59	£ 45,625
0.9	0.2	£ 69,037	13.23	£ 19,105	1.17	£ 16,360	£ 70,090	13.23	£ 18,052	1.17	£ 15,459	£ 63,309	13.73	£ 24,833	0.67	£ 37,044
0.8	0.2	£ 70,083	13.19	£ 18,059	1.21	£ 14,984	£ 71,127	13.19	£ 17,015	1.21	£ 14,118	£ 65,681	13.65	£ 22,461	0.75	£ 29,960
0.7	0.2	£ 71,129	13.15	£ 17,013	1.24	£ 13,690	£ 72,164	13.15	£ 15,978	1.24	£ 12,857	£ 68,147	13.57	£ 19,995	0.83	£ 24,024
0.6	0.2	£ 72,175	13.12	£ 15,966	1.28	£ 12,472	£ 73,201	13.12	£ 14,941	1.28	£ 11,670	£ 70,706	13.48	£ 17,436	0.92	£ 18,989
0.5	0.2	£ 73,221	13.08	£ 14,920	1.32	£ 11,323	£ 74,238	13.08	£ 13,904	1.32	£ 10,551	£ 73,361	13.39	£ 14,780	1.01	£ 14,671
1	0.3	£ 72,579	13.14	£ 15,563	1.26	£ 12,341	£ 73,640	13.14	£ 14,502	1.26	£ 11,499	£ 71,871	13.52	£ 16,271	0.88	£ 18,554
0.9	0.3	£ 73,166	13.11	£ 14,976	1.29	£ 11,650	£ 74,219	13.11	£ 13,923	1.29	£ 10,831	£ 73,328	13.46	£ 14,814	0.93	£ 15,878
0.8	0.3	£ 73,753	13.09	£ 14,388	1.31	£ 10,984	£ 74,797	13.09	£ 13,345	1.31	£ 10,188	£ 74,821	13.41	£ 13,321	0.99	£ 13,449
0.7	0.3	£ 74,341	13.06	£ 13,801	1.33	£ 10,343	£ 75,375	13.06	£ 12,767	1.33	£ 9,568	£ 76,351	13.35	£ 11,791	1.05	£ 11,235
0.6	0.3	£ 74,928	13.04	£ 13,214	1.36	£ 9,725	£ 75,954	13.04	£ 12,188	1.36	£ 8,970	£ 77,917	13.29	£ 10,225	1.11	£ 9,212
0.5	0.3	£ 75,515	13.01	£ 12,627	1.38	£ 9,129	£ 76,532	13.01	£ 11,610	1.38	£ 8,394	£ 79,521	13.23	£ 8,621	1.17	£ 7,356
1	0.4	£ 74,973	13.07	£ 13,169	1.33	£ 9,883	£ 76,035	13.07	£ 12,107	1.33	£ 9,086	£ 78,079	13.35	£ 10,063	1.05	£ 9,605
0.9	0.4	£ 75,321	13.05	£ 12,821	1.35	£ 9,498	£ 76,374	13.05	£ 11,768	1.35	£ 8,719	£ 79,006	13.31	£ 9,136	1.09	£ 8,383
0.8	0.4	£ 75,669	13.03	£ 12,473	1.37	£ 9,124	£ 76,713	13.03	£ 11,429	1.37	£ 8,361	£ 79,949	13.26	£ 8,192	1.13	£ 7,233
0.7	0.4	£ 76,017	13.01	£ 12,125	1.38	£ 8,759	£ 77,052	13.01	£ 11,090	1.38	£ 8,011	£ 80,910	13.22	£ 7,232	1.18	£ 6,148
0.6	0.4	£ 76,365	13.00	£ 11,777	1.40	£ 8,403	£ 77,390	13.00	£ 10,751	1.40	£ 7,671	£ 81,887	13.18	£ 6,255	1.22	£ 5,124
0.5	0.4	£ 76,713	12.98	£ 11,429	1.42	£ 8,055	£ 77,729	12.98	£ 10,412	1.42	£ 7,339	£ 82,881	13.13	£ 5,261	1.27	£ 4,155
1	0.5	£ 76,391	13.02	£ 11,751	1.38	£ 8,532	£ 77,452	13.02	£ 10,690	1.38	£ 7,761	£ 81,932	13.24	£ 6,210	1.16	£ 5,350
0.9	0.5	£ 76,597	13.01	£ 11,545	1.39	£ 8,305	£ 77,649	13.01	£ 10,493	1.39	£ 7,548	£ 82,513	13.20	£ 5,629	1.19	£ 4,718
0.8	0.5	£ 76,803	12.99	£ 11,339	1.40	£ 8,082	£ 77,846	12.99	£ 10,296	1.40	£ 7,338	£ 83,102	13.17	£ 5,040	1.23	£ 4,112
0.7	0.5	£ 77,009	12.98	£ 11,133	1.42	£ 7,864	£ 78,044	12.98	£ 10,098	1.42	£ 7,133	£ 83,699	13.14	£ 4,442	1.26	£ 3,529
0.6	0.5	£ 77,215	12.97	£ 10,927	1.43	£ 7,649	£ 78,241	12.97	£ 9,901	1.43	£ 6,931	£ 84,305	13.10	£ 3,837	1.29	£ 2,969
0.5	0.5	£ 77,421	12.96	£ 10,721	1.44	£ 7,438	£ 78,438	12.96	£ 9,704	1.44	£ 6,733	£ 84,918	13.07	£ 3,224	1.33	£ 2,430

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations presented in the ACD fail to take account of several important points in relation to the management of LSCD within the NHS:

- It is acknowledged in the ACD that the clinical experts stated 3-5% of patients undergoing CLAU would have permanent serious damage to the donor eye and that the estimated success rate for CLAU in the affected eye was 50%. It is therefore clear that, even in expert hands, 50% patients treated with CLAU will be left with an affected eye unsuccessfully treated and for 3-5% of these, their only previously healthy eye will be left with permanent serious damage as a consequence of the CLAU procedure. It is also acknowledged in the ACD that the clinical experts were not aware of any instances of damage to the donor eye for Holoclar. Given that this is how clinical experts in LSCD will likely also council their patients, a significant number of patients with unilateral LSCD therefore refuse to undergo CLAU due to the combination of an uncertain outcome in the affected eye (50% failure rate) and the risks of permanent serious damage to the unaffected eye (3-5%). The ACD acknowledges that the clinical experts stated that patient refusal to undergo CLAU was often the case.

- It is acknowledged in the ACD that the clinical experts explained finding a source of donor tissue can be problematic. It cannot therefore be assumed that every patient with LSCD has an available and willing (ideally first degree) relative prepared to act as a donor for lr-CLAL. Furthermore, the risk of serious permanent damage to the donor eye is 3-5%, and even if initially successful the procedure will fail within 5 years. After this time the patient at best returns to their status prior to lr-CLAL (although due to the recognised side effects of the associated immunosuppression this should not be assumed) and 3-5% of previously healthy donors have permanent serious damage to their eye. Understandably not all potential donors are willing to accept this risk to their own eye for a benefit to their relative that even if initially successful will not last beyond 5 years.

- Some patients may be unsuitable to receive lr-CLAL due to contra-indications to the associated immunosuppression that is required for this procedure, which should be continued until the point in time that the graft ultimately fails, i.e. up to 5 years. As described in the company submission, systemic immunosuppression with mycophenolate is the immunosuppressant of choice for lr-CLAL in patients with LSCD(8). However, this cannot be given during pregnancy or to women of child-bearing potential who are not using highly effective contraception. In addition, elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and gastrointestinal haemorrhage and pulmonary oedema (9).

- For the reasons stated above, some specialist ophthalmology centres do not offer either CLAU or lr-CLAL and these procedures are therefore not available to all patients within the NHS. The ACD acknowledges that one clinical expert stated that they no longer offered CLAU. However, this is not a fully accurate description of what was expressed by the clinical expert who stated that they considered CLAU and lr-CLAL (and KLAL) to be questionable both on clinical and, in the case of lr-CLAL, ethical grounds such that they do not offer any of these procedures and have not for many years. Furthermore, the other clinical expert stated that they had undertaken only 5 CLAU procedures throughout their entire professional career.

The recommendations proposed in the ACD do not therefore take account of cases where patients refuse CLAU, and/or an available and willing living-related donor cannot be identified, and/or lr-CLAL is unsuitable and/or patients are being treated in NHS centres where these procedures are not recommended by their treating ophthalmologist. The current recommendations do not provide any explicit guidance for these patients. Indeed, the implicit outcome is that these patients would not receive Holoclar and by default be manged with best supportive care (BSC), which it is agreed is not cost-effective and indeed dominated.

By revisiting the UK incidence and prevalence data for moderate to severe LSCD due to chemical or physical burns it is clear that, contrary to the opinion of the ERG, this group of patients is very real within the NHS. The estimated incidence of new cases of severe chemical corneal injury in the UK is 0.02 in 100,000 people (13 new cases per year) with a mean age at the time of injury of 33.8 years (median 38.5 years, range 10-59 years), i.e. encompassing the child-bearing years for women (6). In contrast, the prevalent population believed to match the indication for Holoclar is estimated at 121 patents in the UK (10). Clearly if CLAU and lr-CLAL, which have been available for many years, were able to meet the needs of, were suitable for and accepted by all patients with moderate to severe LSCD due to chemical and physical burns (and their ophthalmologists), the UK prevalence figure would be far closer to the incidence figure. As this is not the case, there are clearly a significant number of patients in the UK who have either been unsuccessfully treated with the current technologies, are unsuitable for the current technologies, not offered the current technologies by their ophthalmologists or are choosing not to be treated with the current technologies due to concerns over risks to their own health and/or that of a relative, and therefore are being managed with the least cost-effective of all options, i.e. BSC.

However, all these points could be addressed by modification of the recommendations as follows:

> 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 (defined by the presence of superficial corneal

neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity) after eye burns, only if:

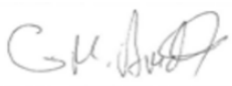
- only 1 eye is treated and
- they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft *or physician judgement is that these procedures are unsuitable* when 1 eye is affected, or
- they have already had a conjunctival limbal allograft *or 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.

It is only with these (or similarly worded) amendments incorporated are the recommendations a sound and suitable basis for guidance to the NHS and thereby ensure that certain groups of patients do not by default, because the recommendations make no provision for them, receive a treatment (i.e. BSC) that has been shown out of all the options considered in this technology appraisal to be the least cost-effective for the NHS.

Finally, Chiesi notes the proposal within the ACD to review this guidance three years after its publication. Chiesi would like to make the Appraisal Committee aware that the results of the currently ongoing prospective, multinational, multicentre, open label, uncontrolled interventional phase IV study (HLSTM03/HOLOCORE), which is being conducted in at least 65 patients with moderate to severe LSCD (plus 5 paediatric patients as agreed in the approved Paediatric Investigation Plan) will most likely be available in 2021. Chiesi suggests that any review of this guidance would be more meaningful with these data included and therefore would like to request that the Appraisal Committee considers a review of this guidance take place in four years not three.

If you or the Appraisal Committee have any queries regarding Chiesi's comments on the ACD or if anything is unclear, then please do not hesitate to contact me. I look forward to seeing you at the next Appraisal Committee meeting on 16th May.

Yours sincerely,



Greg Amatt
Head of Rare Diseases UK & Ireland
Chiesi Limited

Enclosures:

1. Chiesi Limited. Data on file: Survival Rate Sensitivity Analyses Holoclar v120417.xls. Date of Preparation May 2017.

References:

1. 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.

2. 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.

3. 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.

4. 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.

5. Gardiner MD, Topps A, Richardson G, Sacker A, Clarke A, Butler PEM. Differential judgements about disfigurement: the role of location, age and gender in decisions made by observers. J Plast Reconstr Aesthetic Surg. 2010;63(1):73–7.

6. 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.

7. Reidy A, Minassian DC, Vafidis G, Joseph J, Farrow S, Wu J, et al. Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. BMJ. 1998;316(7145):1643–6.

8. Chiesi Limited. Data on File: Notes from Meeting with Mr Alex Shortt, 22nd June 2016 (CHHOL20160794). Date of Preparation July 2016.

9. Roche Registration Limited. Cellcept 250mg Capsules Summary of Product Characteristics [Internet]. November 2015. Available from: http://www.medicines.org.uk/emc/print-document?documentId=1679

10. Medi-Pragma. Data on File: Limbal Stem Cell Deficiency Market Potential Analysis Summary Report, May 2012.

8 May 2017

The ROYAL COLLEGE of OPHTHALMOLOGISTS

[redacted]

Meindert Boysen
Programme Director, Technology Appraisals
Centre for Health Technology Evaluation
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Dear Meindert

Re: Single Technology Appraisal (STA) Holoclar for treating limbal stem cell deficiency after eye burns [ID899] Appraisal consultation document

Thank you for asking the Royal College of Ophthalmologists to comment on this STA.

There are 3 main issues related to this NICE technology appraisal on HOLOCLAR, as follows:

1. Technical aspects including culture, transportation and clinical outcomes: the RCOphth believes there are no issues on these aspects as Holoclar was approved by the EMA based on a very thorough assessment of their system and data provided by the manufacturer. Their clinical data is mainly retrospective and for this reason the EMA granted license is conditional pending a multi-centre EU wide prospective clinical trial involving 65 patients, including five children and a EU registry. With the data from both studies the EMA will decide in terms of a full license. But this will take another three to four years.

2. Label indication for the product: again, this is clear and the College does not have any issues.

3. Cost: It is a rather expensive treatment. This is understandable as it is a cell therapy. The company has proposed a discounted rate for the U.K. There is some disquiet regarding the high cost however, it will be the only licensed product available in EU.

In summary, this is the first cell therapy approved by the EMA that will be approved at EU member states level widely and as stated above the RCOphth supports it.

Yours sincerely,

[redacted]

30th April 2017

Stephanie Yates
Project Manager
Technology Appraisals - Committee C
National Institute for Health and Care Excellence

Re: 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 Stephanie,

As you were aware I recently served as an expert on the recent NICE committee appraisal of Holoclar. I would like to comment on the appraisal consultation document (ACD) that was issued on 5th April 2017.

The management of Limbal Stem Cell Deficiency (LSCD) is a complex and dynamic process. Reducing this to a single algorithm is very difficult. That being said, the recommendations presented in the ACD fail to grasp several core concepts which I tried to convey at the committee meeting but would appear to have faile. The proposed algorithm for the management of LSCD within the NHS is unworkable and represents a waste of time for all concerned in this process. As it currently stands, the draft guidance will see no patients being treated with Holoclar on the NHS. My reasons for making this assertion are as follows:

- CLAU is not an acceptable choice for the majority of my patients. The panel would appear to have accepted that 3-5% of patients undergoing CLAU would have permanent serious damage to the donor eye and that the estimated success rate for CLAU in the affected eye is approximately 50%. For these reasons CLAU is clearly a less than optimal technique. When I present patients with this data and offer them a limbal stem cell transplant using the CLAU technique they virtually all decline the procedure. I have done 3 of these procedures in the past 4 years despite offering it to approximately 40 patients.

The proposed guidance precludes these patients from receiving Holoclar because they choose not to undergo a procedure which they quite rightly perceive to be high risk and low reward.

- For related reasons to the above, lr-CLAL is also an unacceptable choice for most patients as well as for their relatives who are required to donate tissue. To assume that every patient requiring treatment for LCSD has a blood relative available and willing to act as a donor for lr-CLAL is completely wrong. It is my experience that the risk of serious permanent damage to the donor eye is 3-5%. For these reasons it is my experience that relatives frequently refuse to donate tissue and patients with LSCD frequently refuse to allow them. The proposed guidance placed patients and their family members in a difficult position of being forced to undergo this procedure in order to subsequently gain access to Holoclar.

- Even if the lr-CLAL is successful in the recipient, data from clinical trails show that all of these grafts fail within 5 years unless the recipient is heavily immunosuppressed at great expense and high risk of complications. Several patients have contra-indications to This adds another barrier to patients choosing to undergo lr-CLAL. It is my experience that for these reasons patients choose conservative, supportive management of their LSCD over lr-CLAL. The proposed guidance will place patients in the position of needing to take a risk that they find unacceptable in order to gain access to Holoclar.

- Several tertiary corneal centres in the UK do not offer either CLAU or lr-CLAL and these procedures are therefore not available to all patients within the NHS. For NICE to put a guideline in place which requires surgeons to undertake outdated and ineffective procedures with a low sccess rate seems to me to make little sense and simply increases the cost to the NHS were they to do so.

I strongly urge the committee to reconsider their guidance. If published as is, this will adversely affect real patients by forcing them to have procedures which are outdated and ineffective and place them at increased risk by requiring them to take toxic immunosuppression in order to gain access to Holoclar. In real terms this guidance will place unnecessary and unfair barriers to patients receiving a treatment which ultimately would benefit them and save the NHS money over conservative management.

Lastly, Holoclar offers long term regeneration of the surface of the eye. The results of Prof Rama's NEJM paper in 2014 show that the effect of the therapy appears to be permanent. The insistence of NICE to use a 3% discount is therefore incorrect and a 1.5% discount is clearly warranted in this situation.