NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ciclosporin for treating dry eye disease which has not improved after treatment with artificial tears [ID665]

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:
   - **Santen GmbH**
   - **Royal College of Nursing**

'No comment' response received from the Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - **Professor F C Figueiredo – Clinical Expert, nominated by Santen GmbH**

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRIG)

6. **Evidence Review Group Addendum to Extended figure 6**

7. **Evidence Review Group Addendum**

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

Ciclosporin for treating dry eye disease which has not improved despite treatment with artificial tears

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

Consultee	Comment [sic]	Response
Santen Pharmaceutical	Santen GmbH ("Santen") would like to thank both Liverpool Reviews and Implementation Group (LRIG) as well as the NICE appraisal committee for their detailed and balanced review of the evidence presented as part of ID665. We welcome the opportunity to comment on the draft Appraisal Determination Consultation (ACD) document and also the opportunity to resubmit additional evidence, as well as clear guidance as to what is requested. We further appreciate the committee's recognition that patients with severe dry eye disease are close to complete corneal blindness and the high unmet medical need for effective, licenced treatments in the UK. Ciclosporin A (CsA) has the ability to improve ocular surface damage and reduce inflammation in dry eye disease (DED) patients with severe keratitis, which is thought to help prevent disease progression1. Unlicensed ophthalmological preparations of CsA have been used for some time in UK clinical practice, allowing physicians and patients to effectively manage severe DED. However, with the recent discontinuation of the Moorfields Pharmaceuticals 2% eye drops, access to ophthalmologic preparations of CsA is increasingly difficult for DED patients in the UK, adding to the challenge and cost of effectively managing the condition. At £72 per month, Ikervis not only has a considerably lower acquisition price than other available CsAs but also has the additional benefit of a convenient once daily method of administration, and, with NICE approval, avoids the worst case scenario where patients and physicians are unable to access the treatment they require, particularly in cases where short bursts of corticosteroids (CS) have failed to ameliorate the condition. *The additional evidence submitted by Santen Pharmaceutical in response to the Committee's request in the appraisal consultation document is not reproduced here but can be accessed through the Committee Papers*	Comment noted. The Committee considered comments from the clinical experts that severe dry eye disease is an inflammatory disease associated with long-term disease progression. The Committee noted that ciclosporin showed a statistically significant difference in reducing HLA-DR, a measure of inflammation, and in change in CFS, a measure of corneal damage, and concluded that these outcomes were clinically relevant (please see section 4.6 in the FAD). The Committee noted comments from the company stating that 2% CsA eye drops developed by Moorfields Pharmaceuticals are no longer available in the NHS. However, it heard from the ERG that another 2% CsA eye drop formulation could be sourced. The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available. It therefore discussed the ERG's and the company's cost-minimisation analyses comparing ciclosporin (Ikervis) with the other ciclosporin formulations. The Committee considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations (see sections 4.2 and 4.16 in the FAD).

1. ID665 ciclosporin ACD comments table to PM for publication (no ACiC)

Consultee	Comment [sic]	Response
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: i) **Has the relevant evidence been taken into account?** Our members suggest that the evidence considered seems comprehensive.	Comment noted.
	ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Our members consider that the case against has been well made.	Comment noted. Having considered additional information presented in response to consultation, the Committee considered that the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that, on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears (see section 4.16 in the FAD).

Consultee	Comment [sic]	Response
	iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Our members at this moment in time support the committee's conclusion based on the evidence presented. Our members commented that they would, however, have liked more detail on the patient's viewpoint. They noted that there are lay members on the appraisal committee, but it is not clear if these lay members are patients. On page 47 it states that patient experts were selected but none were listed as having contributed their personal view on the use of Ciclosporin for treating of dry eye disease. A patient/service user would have added a further perspective. They also note that the committee has asked NICE to request further analyses from the company, which should be made available for the second Appraisal Committee meeting. The RCN look forward to receiving the report from the second appraisal committee meeting and would welcome guidance to the NHS on the use of this health technology.	Comment noted. NICE invited patient organisations relevant to the appraisal to participate in this appraisal as consultees and commentators. Please see section 8 of the FAD for a list of the organisations that accepted the invitation to participate in this appraisal as consultees and commentators. Please see the Committee Papers for a list of the organisations invited. The Committee noted that the company had provided the amendments it requested in the appraisal consultation document by presenting an updated economic model that compared ciclosporin plus corticosteroids (if needed) and artificial tears with vehicle plus corticosteroids (if needed) and artificial tears (see section 4.10 in the FAD).
	iv) **Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. Please see the Equality Impact Assessment form.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Santen Pharmaceutical	**Has all of the relevant evidence been taken into account?** It is rather important to take into consideration the seriousness of severe dry eye disease (DED) associated with keratitis (i.e. significant impact on patient's QoL and high risk of serious ocular surface infection if left untreated) where IKERVIS has clearly demonstrated a significant benefit (i.e. improvement of keratitis)	Comment noted. The Committee considered comments from the clinical experts that severe dry eye disease is an inflammatory disease associated with long-term disease progression. The clinical experts also stated that people with severe dry eye disease are close to having complete corneal blindness and that any treatment which offers a benefit in terms of reducing inflammation should be considered clinically relevant. The Committee noted that ciclosporin showed a statistically significant difference in reducing HLA-DR, a measure of inflammation, and in change in CFS, a measure of corneal damage, and concluded that these outcomes were clinically relevant (see section 4.6 in the FAD).
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • **Page 12:** *Patients with temporary or permanent punctal plugs were assumed to not use artificial tears.* This is an incorrect concept. • **Page 16:** *The ERG stated that it is unclear whether CFS-OSDI response is a clinically relevant end point.* It is indeed relevant • **Page 17:** *The ERG considered that there was no sufficient evidence available to support a cost-effectiveness analysis of ciclosporin compared with established clinical practice in the NHS for severe dry eye disease*. The main point here is the significant improvement of keratitis and HLA expression in patients with severe dry eye associated with keratitis. This is a high risk group of patients given their serious vulnerability to develop secondary ocular surface infection and the impaired QoL given high	Comments noted. The company's updated model, in response to the Committee's request in the appraisal consultation document, assumed that artificial tears may be used alongside punctal plugs (see sections 3.37 and 4.10 in the FAD). The Committee heard from the clinical experts stated that in clinical practice there is no clear definition for response and non-response, but that the greater the benefit in CFS the more likely this would have a beneficial effect in slowing disease progression (see section 4.7 in the FAD). The Committee noted that ciclosporin showed a statistically significant difference in reducing HLA-DR, a measure of inflammation, and in change in CFS, a measure of corneal damage, and concluded that these outcomes were clinically relevant (see section 4.6 in the FAD).

Nominating organisation	Comment [sic]	Response
	symptomatology and poor sight. • **Page 22:** *The Committee also understood that in clinical practice ciclosporin would be given in combination with corticosteroids (if needed) and artificial tears, and concluded that this represents established clinical practice without ciclosporin, that is, the definition of the comparator in the final NICE scope.* Not necessarily?	The Committee heard from the clinical experts stated that ciclosporin is sometimes started at the same time as steroid treatment because ciclosporin has a slower onset of action and it will start to show an effect by the time steroid treatment is stopped. They also noted that treatment with corticosteroids can be restarted again if needed. The clinical experts explained that corticosteroids would be considered as an additional treatment to ciclosporin if needed and that they have the effect of allowing people to continue treatment with ciclosporin for longer (see section 4.1 in the FAD).
	• **Page 23:** *Optimmune ointment is more widely used in the NHS for people with severe dry eye disease but that many people are not willing to have treatment because of its veterinary marketing authorisation. The clinical experts also noted that it can only be used at night because it causes blurred vision and that there are some people who cannot tolerate ointments.* Not entirely true	Comment noted. Please see amended section 4.2 in the FAD.
	• **Page 25:** *The clinical experts also stated that people with severe dry eye disease are close to having complete corneal blindness* This is not necessarily true. It is an extremely rare event/complication of DED.	Comment noted. Please see amended section 4.6 in the FAD.
	• **Page 26:** *However, it was aware that the ERG considered that the clinical relevance of this revised definition of response was unclear and that it excluded the level of benefit which most favoured the vehicle group.* The indication for IKERVIS use is very specific as per company's proposal. This is rather important to tackle the more severe and most difficult patients with a more sever degree of dry eye disease associated with significant keratitis.	Ciclosporin is recommended as an option, within its marketing authorisation, for treating severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes (see section 1.1 in the FAD).
	• *The clinical experts stated that in clinical practice there is no clear definition for response and non-response, but that the greater the benefit in CFS the more likely this would have a beneficial effect in slowing disease progression.* Often associated with improvement of symptoms that is highly important that would consequently improve patient's QoL.	Comment noted. Please see amended section 4.7 in the FAD.

Nominating organisation	Comment [sic]	Response
	• *The Committee had reservations about all the post hoc analyses presented by the company and considered that these analyses were not robust enough to reach a conclusion on the relative clinical effectiveness of ciclosporin compared with the vehicle*. In my view the pos hoc analysis is rather important as it showed a significant improvement of keratitis associated with dry eye disease. This is highly relevant given the risk of secondary infection associated with keratitis in patients with dry eye. All dry ye patients are more vulnerable to ocular surface infection in particular to bacterial keratitis due to a decreased ocular surface protection provided by a normal tear film. • **Page 27:** *Committee concluded that the company's model was of limited relevance because it failed to show the cost effectiveness of ciclosporin compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears*. It is rather important to highlight that our most recent day-to-day management experience in clinical practice has been influenced by the post-RESTASIS usage in patients with dry eye in other parts of the world where RESTAIS is available and the design of the SANSIKA study was to use a single treatment in addition to artificial tears for the management of DED that has proved to be more effective in patients with severe DED associated with significant keratitis. • *The Committee heard from the clinical experts that in clinical practice treatment is not stopped because of adverse effects.* This is not necessarily correct as patients do stop treatment in the presence of side effect, however we do try to persuade patients to persevere with topical treatment in the assumption that the local side effect will improve with time or completely resolve. Local AEs are largely thought to be transient in DED and have a very limited impact on patient's QoL. • **Page 29:** *The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life* There is no evidence of a log term-effect of cyclosporin adverse event on patient QoL • **Page 37:** *The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life* As previously reported most topical side effect are transitory and of no long-term importance.	Comment noted. The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available (see section 4.16 in the FAD). The Committee concluded that it was unclear when treatment with ciclosporin would be stopped in clinical practice because the potential impact of corticosteroids in stopping rates had not been included in the company's updated model (see section 4.12 in the FAD). The Committee noted comments from a clinical expert stating that adverse effects with ciclosporin are transient and have limited impact on quality of life (see section 4.13 in the FAD).

Nominating organisation	Comment [sic]	Response
	• *The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice.* There is no hard/published evidence regarding a uniform established clinical practice. Therefore, it would be erroneous and possibly inappropriate to expect that we do have uniform and well established clinical practice for the management of patients with severe dry eye associate with severe keratitis.	The Committee considered that the company's original and updated models lacked relevance because the comparator used was vehicle rather than corticosteroids (if needed) and artificial tears, which is considered established clinical practice. The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available (see sections 4.15 and 4.16 in the FAD).
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Unlicensed cyclosporin A is routinely used in NHS ocular surface clinics across the UK. A failure to support IKERVIS use in the NHS despite EMA MA will maintain a system of continued use of unlicensed cyclosporin A in the UK that is unjustifiable given the fact that the rest of the world is using a licensed cyclosporin A compound regularly to treat patients with dry eye disease	Comment noted. The Committee noted comments from a clinical expert and the company that if ciclosporin (Ikervis) were not recommended for use in the NHS, other ciclosporin formulations that do not have marketing authorisation in the UK (and are associated with higher costs) would continue to be used instead. The Committee considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that, on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears (see section 4.16 in the FAD).

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional	General	The UK Ophthalmic Pharmacy Group's comments, endorsed by the Royal Pharmaceutical Society are as follows:	Comment noted. The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		Topical ocular ciclosporin has been used in ophthalmology for many years for a wide range of indications including the licensed use for IkervisÂ® â€˜Treatment of severe keratitis in adult patients with dry eye disease which has not improved despite treatment with tear substitutesâ€™. There is a wealth of evidence to support the use of topical ciclosporin in addition to the SANSIKA and SICCANOVE trials which relate specifically to the IkervisÂ® product (see attached prepared by Edward Hindle, 2014) Initially an unlicensed preparation containing ciclosporin 2% in arachis oil manufactured by Moorfields Pharmaceuticals was used but as this was poorly tolerated, many prescribers turned to the veterinary product OptimmuneÂ® eye ointment containing ciclosporin 0.2% and then when Allerganâ€™s RestasisÂ®, single dose eye drops containing ciclosporin ophthalmic emulsion 0.05% became available in the USA, this was imported via a pharmaceutical wholesaler. Moorfields Pharmaceuticals then produced a multidose preservative-free formulation of ciclosporin 0.06% until the unit closed last year. All these products, due to their wide use were or are included in the Drug Tariffâ€™s list Part VIIIB - Arrangements for payment for Specials and Imported Unlicensed Medicines Ciclosporin 2% eye drops (Moorfields Pharmaceuticals) from November 2012 to May 2015; last price @ May 2015 Â£126.53 for 10ml Ciclosporin 0.2% eye ointment from November 2012 to date; current price Â£80.69 for 3.5g Ciclosporin 0.05% unit dose eye drops (RestasisÂ®, imported) from November 14 to date; current price Â£7.57 for each 0.4ml unit. With a licensed frequency of one drop every 12 hours this equates to Â£454.20 for 30 daysâ€™ treatment. Ciclosporin 0.06% multidose eye drops (Moorfields Pharmaceuticals) from November 14 to May 15 (last price @ May 2015 Â£53.03 for 10ml). There is no standard in use shelf life for multidose preservative-free eye drops so	comparison with other ciclosporin formulations available. The Committee considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that, on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears (see section 4.16 in the FAD).

Role*	Section	Comment [sic]	Response
		with some pharmacies allocating 24 hours shelf life and others 7 daysâ€™ shelf life this equates to Â£212 to Â£1,484.84 for 28 daysâ€™ treatment. Members of the UK Ophthalmic Pharmacy Group were delighted to hear that Santen are to bring a licensed topical ophthalmic preparation of ciclosporin to the market. Many Hospital Trustsâ€™ formularies contain one or both preparations of ophthalmic ciclosporin purchased as unlicensed products and we look forward to using the licensed preparation for both the licensed indication and the many as yet unlicensed indications for the product instead of the unlicensed product in accordance with the MHRAâ€™s guidance, the General Medical Councilâ€™s guidance and the Royal Pharmaceutical Societyâ€™s guidance on use of unlicensed preparations. With the forthcoming launch of IkervisÂ®, we expect Trust Drug & Therapeutics Committees/Medicines Management Committees to restrict the prescribing of IkervisÂ® in the hospitals, possibly to consultant ophthalmologists specialising in corneal diseases, and Area Prescribing Committees restricting to continuation of therapy by General Practitioners following specialist initiation. Thus, we expect prescribing of IkervisÂ® to be strictly limited and would support this approach to enable ophthalmic pharmacists to supply a licensed product rather than the very costly unlicensed products currently in use. We support the statement in the attached summary updated in view of the impending launch of a licensed product â€˜The licensed ciclosporin product should be available to patients who have been assessed by an appropriate specialist and this should be available to be continued in primary careâ€™. Edward Hindle, Lucy Titcomb, Jacqueline Jones, Elaine Mann UK Ophthalmic Pharmacy Group July 15 We have a pdf document reviewing ocular uses of ciclosporin to accompany comment 1 - please advise how to submit this?	

Role*	Section	Comment [sic]	Response
Professional body for optometrists	General	We are of the opinion that the recommendations are not discriminatory against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. We wanted to raise our concern regarding the definitions of Dry Eye Disease (DED) that were used in the two studies considered. They were based on a combination of clinical features and symptoms, for which there is indeed a well-established precedent. However in DED there is a notorious lack of correlation between signs and symptoms (a fact which is acknowledged in the document). In addition, it is not apparent in either study that the type of DED had been characterised. DED is divided into aqueous-deficient and evaporative types, and the two types have different pathogenic mechanisms. (Confusingly however, the two types may co-exist.) In that the SICCANOVE study included a measurement of tear break-up time, the possibility of evaporative DED was recognised, but this does not appear to apply to the inclusion criteria of the SANSIKA study. The provisional recommendations are sound and are a suitable basis for guidance to the NHS. Further evidence on the efficacy and cost-effectiveness of ciclosporin in the management of severe dry eye is required before this medicine can be recommended within the NHS. We are aware that ciclosporin for ophthalmic use is not currently available in the UK and its use is not recommended in any guidance published by the College of Optometrists. We agree that all of the relevant evidence has been taken into account. The findings of the NICE evidence synthesis review are consistent with a recently published systematic review by Saccheti et al http://www.ncbi.nlm.nih.gov/pubmed/24344232 We have considerable experience of the use of Optimmune ointment in	Comments noted. The Committee noted that ciclosporin plus artificial tears did not show any differences compared with the vehicle plus artificial tears in any measure for symptoms. It heard from the company that this could be because of the well-known poor correlation between signs and symptoms and because of the possible beneficial effect of the vehicle on its own (see section 4.5 in the FAD). Full details of all the evidence can be found in the Committee papers (see section 3.50 in the FAD). The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available. The Committee considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that, on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears (see section 4.16 in the FAD).

Role*	Section	Comment [sic]	Response
		severe chronic allergic eye disease (i.e. Vernal and Atopic Keratoconjunctivitis). Experience suggests that very few patients are alarmed by the prospect of using a veterinary product if the reasons for its prescription are carefully explained by the clinician. The real problem comes with the continuation of supplies when the GP refuses to prescribe a veterinary product because it is not on the list of prescribable drugs. Ointment does cause some blurring of vision - perhaps for 20 minutes or so - and this is generally well tolerated by patients who appreciate that the benefits of treatment outweigh the transitory side-effects. It is true that ointment base (which contains lanolin) is not tolerated by a very small proportion of patients. We are of the opinion that this paragraph may dismiss or at any rate discourage the possibility of using a very important source of topical ciclosporin, namely Optimmune ointment. We agree that the summary of clinical effectiveness is reasonable interpretations of the evidence. We agree that the summary of cost effectiveness is reasonable interpretations of the evidence.	The clinical experts also noted that Optimmune ointment is more widely used in the NHS for people with severe dry eye disease but that some people hesitate to have treatment because of its veterinary marketing authorisation. The Committee concluded that it was reasonable to assume that the different ciclosporin formulations would show similar efficacy (see section 4.2 in the FAD).

Role*	Section	Comment [sic]	Response
Chief Executive International Glaucoma Association (Medical Charity)	General	The International Glaucoma Association, as representative of many glaucoma patients where dry eye is not uncommon, is concerned now Ikervis is a licensed product, the un-licensed ciclosporin drops will be withdrawn and leave the prescriber and the patients with no like for like alternative to control their dry eye. As the un-licensed ciclosporin drops have been 'a last alternative' to gain relief for many patients this would be a regrettable situation. We trust the consultation committee will take this into consideration when making their judgement.	Comment noted. The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available. The Committee noted comments from a clinical expert and the company that if ciclosporin (Ikervis) were not recommended for use in the NHS, other ciclosporin formulations that do not have marketing authorisation in the UK (and are associated with higher costs) would continue to be used instead. The Committee considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that, on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears (see section 4.16 in the FAD).

The following consultees/commentators indicated that they had no comments:
Department of Health

Ciclosporin for the treatment of severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes [ID665]: Response to Appraisal Committee Determination

Introduction

Santen GmbH ("Santen") would like to thank both Liverpool Reviews and Implementation Group (LRIG) as well as the NICE appraisal committee for their detailed and balanced review of the evidence presented as part of ID665. We welcome the opportunity to comment on the draft Appraisal Determination Consultation (ACD) document and also the opportunity to resubmit additional evidence, as well as clear guidance as to what is requested.

We further appreciate the committee's recognition that patients with severe dry eye disease are close to complete corneal blindness and the high unmet medical need for effective, licenced treatments in the UK. Ciclosporin A (CsA) has the ability to improve ocular surface damage and reduce inflammation in dry eye disease (DED) patients with severe keratitis, which is thought to help prevent disease progression[1]. Unlicensed ophthalmological preparations of CsA have been used for some time in UK clinical practice, allowing physicians and patients to effectively manage severe DED. However, with the recent discontinuation of the Moorfields Pharmaceuticals 2% eye drops, access to ophthalmologic preparations of CsA is increasingly difficult for DED patients in the UK, adding to the challenge and cost of effectively managing the condition. At £72 per month, Ikervis not only has a considerably lower acquisition price than other available CsAs but also has the additional benefit of a convenient once daily method of administration, and, with NICE approval, avoids the worst case scenario where patients and physicians are unable to access the treatment they require, particularly in cases where short bursts of corticosteroids (CS) have failed to ameliorate the condition.

The committee has requested that the following additional work be undertaken and submitted to the Institute for consideration at the next committee meeting:

- An indirect comparison of the clinical effectiveness of CsA plus CS (if needed) and artificial tears (AT), and that of CS (if needed) and AT.

- An economic model comparing the cost effectiveness of CsA+CS (if needed) and AT, with that of CS (if needed) and AT. This cost effectiveness analysis should include:
    - the original SANSIKA Corneal Fluorescein Staining – Ocular Surface Disease Index (CFS-OSDI) definition of response (that is, improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI)
    - an evidence based treatment stopping rates with CsA+CS (if needed) and AT
    - changes to resource use and costs reflecting:
    - that AT may be used alongside punctal plugs
    - both a baseline average and a 6 month average for the number of artificial tear drops used per day, for both treatment groups
    - the assumption that CsA is dispensed and costs are incurred monthly
    - sensitivity analyses using different utility values for response by treatment group
- a subgroup analysis for people with Sjögren's syndrome and severe dry eye disease

The work requested is presented in the remainder of this document. We have tried to respond to all of the requests made by the appraisal committee and present here revised economic analyses based on our best attempts in each case. In section A we present the results of a systematic literature review (SLR) undertaken to identify comparative evidence for CS used in the context defined above on which to base the requested indirect comparison. Section A also contains the results of the indirect comparison.

Section B of this document details the amendments made to the economic model in order to perform all additional analyses requested by the Institute. It also includes further analyses showing that the more stringent post-hoc response definition is a better predictor of utility than the original trial definition or randomised treatment.

The revised cost-effectiveness results generated using the updated model, are presented in Section C of this document. Across all scenarios, incremental costs range by less than £1,200 and incremental QALYs by 0.05. The model is, however, highly sensitive to small changes in costs and QALYs, and these relatively minor fluctuations preclude ICERs which range from £10,670 to £64,617 per QALY gained. Crucially, when using the response definition that is statistically the best predictor of utility benefit, the ICER is £14,517 per QALY gained.

To aid readability of this document we have presented technical supportive material for all of these analyses in appendices.

Section A: SLR and indirect comparison [CsA+CS (if needed) and AT, CS (if needed) and AT]

The existing SLR was updated and in order to meet the Institutes primary request – assessing the relative efficacy of the following treatment options via an indirect comparison:

- CsA+CS (if needed) and AT
- CS (if needed) and AT

The SANSIKA trial, considered by Santen, LRIG, and the Committee as the most appropriate trial of CsA in patients with severe dry disease was a randomised controlled trial of:

- CsA (more specifically, Ikervis®) 1 mg/mL, an excipient ("Vehicle") + AT
- Vehicle + AT

The use of corticosteroids prior to, and during the course of, the SANSIKA trial were prohibited as outlined in the trial exclusion criteria (SANSIKA CSR, pg. 44):

'Use of topical corticosteroids, antibiotics, pilocarpine, antihistamines, or BAK-preserved IOP lowering medications within 30 days before the Screening Visit. These treatments were also prohibited during the course of the study.'

As stated in section 4.4 of the draft ACD it is acknowledged that vehicle is not commercially available but is considered similar to the artificial tear Cationorm® (containing: Cetalkonium Chloride; Glycerol; Mineral Oil; Poloxamer 188; Tromethamine; Tromethamine Hydrochloride; Tyloxapol)).

The clinical systematic review presented with the company's submission identified one randomised controlled trial, which included treatment with corticosteroids (Table 1):

Table 1: relevant studies reported in original Santen submission

Author	Title	Treatment composition
Jee et al[2]	Antioxidant and Inflammatory Cytokine in Tears of Patients with Dry Eye Syndrome Treated with Preservative-free vs. Preserved Eyedrops	Preservative-free 0.1% sodium hyaluronate, 0.1% fluorometholone and 0.05% CsA (Restasis®) eye drops vs. Preserved 0.1% sodium hyaluronate, 0.1% fluorometholone and 0.05% CsA (Restasis®) eye drops

The systematic review was updated on 11th May 2015 to ascertain whether any additional randomised controlled trials of patients with severe dry eye disease treated with corticosteroids had been published since the search was last conducted (21st July 2014).

Of the three new studies that had been published meeting the eligibility criteria, one included treatment with corticosteroids (Table 2). Key characteristics of this study were that only patients with Sjögren's Syndrome patients were enrolled and patients were instructed to abstain from the use of topical ophthalmic medications for at least 2 weeks before the study'. In contrast, the SANSIKA wash out period allowed the use of unpreserved artificial tears, whilst all other concomitant treatment was stopped.

Table 2: relevant studies identified by updated SLR

Author	Title	Treatment composition
Lin et al[3]	Topical fluorometholone treatment for ocular dryness in patients with Sjögren syndrome: a randomized clinical trial in China. Medicine (Baltimore).	0.1% flurometholone + 0.1% sodium hyaluronate vs. 0.5% ciclosporin (hospital formulation) + 0.1% sodium hyaluronate

Indirect comparisons between two treatments for which there is no head-to-head evidence are predicated on a common comparator arm in which patients are broadly homogeneous and also a connected network of trial comparisons. As we did not have access to the patient level data from these two studies described above, we considered three possible approaches to conducting the requested indirect comparison:

- Dose equivalence between CsA doses
- Connection via fluorometholone (corticosteroid)
- Connection via fluorometholone (corticosteroid) and vehicle

Each of these are summarised below.

Dose equivalence between ciclosporin doses

The proposed network diagram for this option is presented in Figure 1. Pre-clinical studies conducted by Santen indicate that there is improved bioavailability with CsA 1 mg/mL versus lower doses of CsA (Restasis® 0.05% CsA). Following the phase II dose finding study conducted by Santen only the Ikervis 1 mg/mL dose was continued through to phase III trials and European Medicines Agency (EMA) approval was only provided to the 1 mg/mL dose. It was therefore not thought appropriate to pool the doses of CsA to facilitate an indirect comparison.

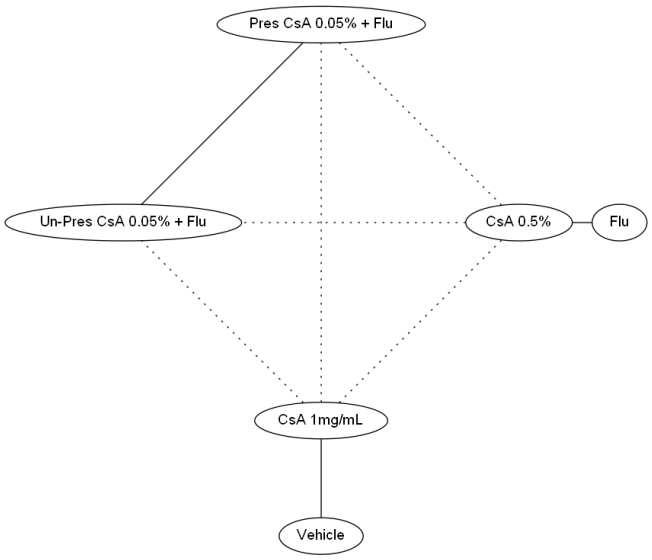

Figure 1 Indirect comparison consideration 1 – dose equivalence of CsA

Connection via fluorometholone (corticosteroid)

The proposed network diagram for this option is presented in Figure 2. The clinicians present at the first Committee meeting were clear in stating that in usual clinical practice CsA would be used with corticosteroids as required hence the request by the Committee to consider CsA + corticosteroids as required as a comparator. As stated above, SANSIKA did not allow the use of corticosteroids during the study; therefore the treatment arm is CsA alone. Given the comments by the clinicians at the Committee meeting it was not considered appropriate to pool CsA alone with treatment arms of CsA + corticosteroids as required so a connection to SANSIKA could not be made.

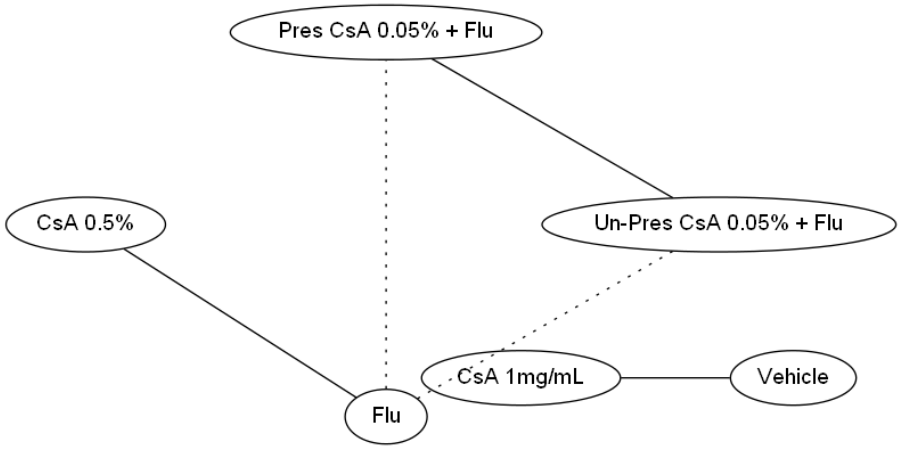

Figure 2 Indirect comparison consideration 2 – connection via fluorometholone (corticosteroid)

Connection via fluorometholone (corticosteroid) and vehicle

The proposed network diagram for this option is presented in Figure 3. As stated in the draft ACD document (section 4.4) vehicle is considered comparable with the artificial tear Cationorm® which does not include any active agents. It was therefore not thought appropriate to bridge CsA+CS (if needed) + AT tears to CS (if needed) + AT via the vehicle + AT and fluorometholone + AT to facilitate an indirect comparison.

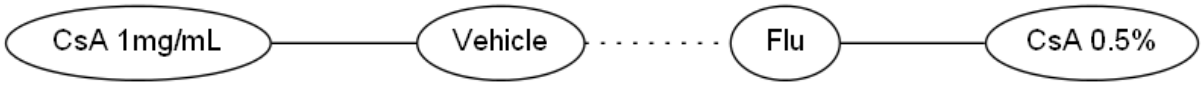

Figure 3 Indirect comparison consideration 3 – connection via fluorometholone (corticosteroid) and vehicle

Conclusion

We believe that given the methodological problems shown it was not possible to undertake a robust indirect comparison as requested by the committee.

Section B: Technical changes made to the Santen economic model in light of suggestions from the NICE appraisal committee

The key technical changes that were made relate to the evidence based stopping rules and the need to perform a subgroup analysis for patients with Sjögren's Syndrome. The latter was undertaken via the inclusion of a binary covariate (yes/no) into a series of regression equations. Two different response definitions were included in the original Santen submission, with aggregate response rates at three and six months taken from the SANSIKA study for both definitions. The response rates used were:

- An improvement of 3 points or more from baseline CFS and improvement of 30% or more from baseline OSDI
- An improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI

The composite CFS-OSDI responder approach consists of a double criteria definition. A sign AND a symptom endpoints are considered corresponding with the objective of defining outcomes measurable for both patients and ophthalmologists. This approach measures simultaneous improvement of both types of endpoints in the same patient and can be viewed as clinically relevant.

The first proposed component of the composite responder analysis is keratitis improvement. Keratitis is a key sign of DED especially in severely affected patients. Therefore maintaining and protecting the ocular surface is one of the main goals for the treatment of these patients[4]. Keratitis is quantified with the modified Oxford scale. It is considered that a two grade or more improvement of CFS on the modified Oxford scale would represent a meaningful change, per patient as it represents at least 50% improvement from Baseline in patients starting with a CFS=4 at baseline (as in SANSIKA).

In the post hoc analysis, the threshold of CFS improvement was at least 3 grades instead of 2. This additional grade of improvement meant that the responders reached grade 1 or less on the modified Oxford scale which is a visual logarithmic scale (i.e. one additional grade of staining corresponds to at least 3.16 fold less dots on the cornea). This change was considered highly clinically relevant since the patients were close to or experiencing corneal clearing.

Standard OLS regression was used to determine which of the post hoc (CFS of at least 3, and OSDI of at least 30%) and pre-specified (CFS of at least 2, and OSDI of at least 30%) response definitions is a stronger predictor of change from baseline utility at 6 months. Results are presented in Table 1 and Table 2 below. With the post-hoc definition of response, the strength of effect on utility (0.104 vs 0.072) is greater and the p-values are more significant (0.023 vs 0.052).

Table 1 OLS regression outputs (post-hoc response definition)

Parameter	Coefficient	s.e.	P-value	95% LCI	95% UCI
Constant	0.001	0.018	0.944	-0.035	0.037
Response = yes (post-hoc definition)	0.104	0.045	0.023	0.014	0.192

Table 2 OLS regression outputs (pre-specified response definition)

Parameter	Coefficient	s.e.	P-value	95% LCI	95% UCI
Constant	-0.002	0.020	0.883	-0.043	0.037
Response = yes (pre-specified definition)	0.072	0.036	0.052	-0.001	0.144

Stepwise model selection methods were used to further test this conclusion, with only response being included in the final model. The outputs from this analysis are presented in Table 3 and Table 4 below. When the two response measures are modelled together the pre-specified response definition is no longer a significant predictor of utility, leaving only the post-hoc. Nonetheless, the Institute requested that additional analyses were undertaken using the latter definition since it was a pre- primary outcome measure in SANSIKA.

Table 3 Predictors of change in utility (post-hoc response not included) - backwards data selection

Backwards data selection					
P =0.5961 ≥ 0.2 removing response (pre-specified definition) = yes					
Parameter	**Coefficient**	**s.e.**	**P-value**	**95% LCI**	**95% UCI**
Response (post-hoc definition) = yes	0.104	0.045	0.023	0.015	0.192
Constant	-0.001	0.018	0.944	-0.035	0.038

Table 4 Predictors of change in utility (post-hoc response not included) - forwards data selection

Forwards data selection					
P =0.0225 ≤ 0.1 adding response (post-hoc definition)= yes					
Parameter	**Coefficient**	**s.e.**	**P-value**	**95% LCI**	**95% UCI**
Response (post-hoc definition) = yes	0.104	0.045	0.023	0.015	0.192
Constant	-0.001	0.018	0.944	-0.035	0.038

Amendments to the approach used to model treatment response rates

Logistic regression was performed using response data at three and six months in order to examine the impact of Sjögren's syndrome on the likelihood of responding to treatment at three and six months. The results from these regression equations are presented in Table 5 and Table 6. The presence of Sjögren's Syndrome was a statistically significant predictor of response at both time points using the pre-specified response definition and at month three using the post-hoc response definition.

Table 5: Logistic regression output (treatment response (pre-specified response definition), including covariate for Sjögren's Syndrome)

Parameter	Coefficient	s.e.	P-value	95% LCI	95% UCI
		Three months			
Constant	-1.510	0.325	0.000	-2.148	-0.873
Ikervis usage	0.655	0.378	0.081	-0.087	1.397
Sjögren's = yes	-1.510	0.325	0.003	-2.148	-0.873
		Six months			
Constant	-0.830	0.277	0.003	-1.373	-0.286
Ikervis usage	0.436	0.323	0.177	-0.197	1.069
Sjögren's = yes	-0.901	0.334	0.007	-1.556	-0.246

Table 6 Logistic regression output (treatment response (post-hoc response definition), including covariate for Sjögren's Syndrome

Parameter	Coefficient	s.e.	P-value	95% LCI	95% UCI
		Three months			
Constant	-2.017	0.388	0.000	-0.527	1.261
Ikervis usage	0.367	0.456	0.421	-0.527	1.261
Sjögren's = yes	-1.032	0.521	0.047	-2.052	-0.011
		Six months			
Constant	-2.172	0.412	0.000	-2.980	-1.364
Ikervis usage	1.082	0.450	0.016	0.198	1.966
Sjögren's = yes	-0.599	0.409	0.144	-1.400	0.203

The final coefficients used in the revised economic model are presented in Table 7 and Table 8 below. For completeness, we have also listed the response rates for all patients in SANSIKA in this study (aggregated across Sjögren's Syndrome status).

Table 7 Response rates (pre-specified response definition) used in revised economic model

Patient group	Three months	Six months
Sjögren's Syndrome receiving Ikervis	11.0%	21.5%
Sjögren's Syndrome not receiving Ikervis	6.0%	15.1%
Non-Sjögren's Syndrome receiving Ikervis	29.8%	40.3%
Non-Sjögren's Syndrome not receiving Ikervis	18.1%	30.4%
All patients receiving Ikervis	21.1%	32.5%
All patients receiving not Ikervis	12.2%	23.7%

Table 8 Response rates (post-hoc response definition) used in revised economic model

Patient group	Three months	Six months
Sjögren's Syndrome receiving Ikervis	6.4%	15.6%
Sjögren's Syndrome not receiving Ikervis	4.5%	5.9%
Non-Sjögren's Syndrome receiving Ikervis	16.1%	25.2%
Non-Sjögren's Syndrome not receiving Ikervis	11.7%	10.2%
All patients receiving Ikervis	12.5%	21.6%
All patients receiving not Ikervis	9.0%	8.6%

Amendments to the approach used to model utility

A similar approach was used to that described above was used to quantify the impact of Sjögren's Syndrome on a patient's Health Related Quality of Life (HRQoL) as characterised using the EQ-5D instrument and calculated using UK tariffs In addition to binary variables (yes/no) treatment and Sjögren's Syndrome, an interaction term between these two variables was included.

Standard OLS regression was used to generate an estimate of the difference in utility at six months compared to baseline. The output from the full model is presented in Table 9 below. The main and interaction terms for Sjögren's syndrome were both non-significant. In contrast, being a responder to therapy was statistically significant. Hence, Sjögren's syndrome did not impact on health related quality of life.

Table 9 results from the full OLS regression analysis (utility change from baseline to month 6)

Parameter	Coefficient	s.e.	P-value	95% LCI	95% UCI
Constant	-0.015	0.038	0.696	-0.090	0.060
Ikervis usage	0.004	0.045	0.935	-0.085	0.092
Sjögren's = yes	0.033	0.057	0.567	-0.079	0.145
Response (pre-specified definition)= yes	0.077	0.038	0.044	0.002	0.153
Treatment* Sjögren's	-0.019	0.072	0.790	-0.161	0.122

Stepwise model selection methods were used to further test this conclusion, with only response being included in the final model. The outputs from this analysis are presented in Appendix 1.

Amendments to the approach used to model treatment discontinuation

Based on additional material from SANSIKA submitted by Santen to the Institute on the 20th February 2015, LRIG raised concerns around the approach used by Santen to model treatment discontinuation. In particular, LRIG were of the opinion that the monthly discontinuation rate for Ikervis plus AT was, in general, higher than for patient receiving AT alone. LRIG also identified an increased discontinuation rate in the first month the Ikervis + AT arm. The Institute requested that Santen incorporate evidence-based treatment stopping rates in the model.

We have worked with the same data provided to the Institute, and used this to inform a formal parametric survival analysis, as opposed to the method used by LRIG based on an analysis of the cumulative hazard functions. In light of the analysis undertaken by LRIG we have looked to include the possibility of an elevated rate in the first model cycle into this analysis. As such, piecewise methods were used, with the unit of time in the statistical analysis set to align with the cycle length in the economic model (0-90 days, greater than 90 days). In line with the original Santen submission and the subsequent LRIG analysis, no "treatment effect" was included, and the two treatment options were modelled independently. Similarly, and again in line with the work undertaken by LRIG, exponential models have been used to generate all outputs.

The results from the survival analysis are presented in Appendix 2. Compared to vehicle, the discontinuation hazard in the first model cycle was close to two times greater with Ikervis. After which, however, treatment discontinuation becomes almost equivalent in both arms of

the trial. Accounting for uncertainty around these estimates highlights that the discontinuation rate between the two arms of the trial is unlikely to differ after 90 days.

Full details are provided in Table 34. With the lack of evidence supporting differential rates of discontinuation post 90 days, the updated economic model adopts a piecewise exponential approach, with a higher initial rate for Ikervis, and a pooled common rate for both arms thereafter. The cycle rates used in the economic model are presented in Table 10, with a comparison of the observed and fitted distributions presented in Appendix 2.

Table 10 evidence based discontinuation rates used in revised economic model

Model cycle	Ikervis + AT	AT alone
One	10.0%	5.8%
Two plus	5.8%	5.8%

Other model amendments made in light of Institute comments/ requests

The use of procedures such as temporary and permanent punctal occlusion in a range of European jurisdictions was reviewed by Clegg in 2006, with an annual implant rate in the UK of less than 1% per dry eye sufferer annually[5]. Due to the small patient count, and in the absence of informative data, a simplification was made in the original submission such that artificial tears would no longer be required following punctal occlusion. We acknowledge the opinion of clinical experts and understand that this may not be reflective of clinical practice and have relaxed the modelling assumption accordingly. As such, people with temporary or permanent punctal plugs are assumed to require artificial tears at a reduced rate, equivalent to that of patients responsive to Ikervis + AT + CS (if needed) and AT + CS (if needed).

Mean drops per eye per day with artificial tears were lower at six months with Ikervis than with vehicle (6.34 vs. 7.32). We accept the comments by both the Institute and LRIG that the difference between treatment arms is non-significant and have amended the approach to modelling artificial tear usage such that an average number of drops of artificial tears per day is assumed for both treatment groups at six months.

It is noted that Ikervis would be prescribed monthly, rather than for three months at the beginning of each model cycle. The economic model has consequently been updated to reflect that Ikervis is prescribed three times per model cycle based on half cycle corrected probabilities reflecting the proportion of patients receiving active treatment with Ikervis at a given point in time.

Section C: Amended cost-effectiveness results

Revised base case analysis

To provide the committee with as much information as possible on which to base any decisions, we have updated the base-case analysis to facilitate a comparison of Ikervis plus CS (if needed) and artificial tears, and of CS (if needed) and AT. In lieu of data, we were forced to make a number of assumptions:

i) CS were included in the model as a cost parameter only.
ii) Flouromethalone (FML, £2.95 for 10ml) and Prednisolone (Pred Forte, £3.66 for 10ml) were the modelled corticosteroids as per clinical opinion.
iii) The impact of corticosteroid use on HRQoL (treatment related glaucoma etc.) was not included.
iv) The treatment duration for CS was set to eight weeks as per the comments from clinical experts reported in the draft ACD.
v) CS were modelled on a response/non-response basis with those who are responsive to treatment (Ikervis + AT or AT alone) less likely to require the anti-inflammatory effects of steroids.
vi) The proportion of responders who require corticosteroid use at some point during a model cycle (three months) was assumed to be 10%, as per clinical opinion.
vii) The proportion of non-responders who require corticosteroid use at some point during a model cycle (three months) was assumed to be 30%, as per clinical opinion.

Tables 11 to 16 detail the incremental cost-effectiveness following technical changes discussed in Section B and stratified by the presence/absence of Sjögren's syndrome. For all patients over a lifetime horizon using the post-hoc response definition, Ikervis is expected to increase quality of life by 0.05 QALYs at an additional cost of £709 generating an ICER of £14,517 per QALY gained. For all patients using the pre-specified response definition, the ICER is £45,554 per QALY gained.

Dry eye disease patients with Sjögren's syndrome are difficult to treat population representing a subset of the general dry eye population. Although Ikervis demonstrated an improvement relative to vehicle using in patients with Sjögren's syndrome, the differences in incremental cost-effectiveness between the three subgroups is small, with ICERs ranging by

less than £2,500 per QALY gained with the post-hoc response definition and less than £1,000 with the pre-specified. In patients with Sjögren's syndrome, the ICERs of Ikervis + AT vs AT without ciclosporin are £16,231 per QALY gained with the post-hoc response definition and £44,874 with the pre-specified. For patients without the condition, the ICERs are £13,850 per QALY gained with the post-hoc response definition and £45,814 with the pre-specified.

Table 11 Revised results generated using all alterations listed in section B with CS (if required) – All patients (post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,531	10.09
AT (no ciclosporin)	£15,882	10.04
Difference	£709	0.05
ICER per QALY gained	£14,517 per QALY gained	

Table 12 Revised results generated using all alterations listed in section B with CS (if required) – Sjögren's syndrome patients (post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,468	10.07
AT (no ciclosporin)	£15,877	10.03
Difference	£590	0.04
ICER per QALY gained	£16,231 per QALY gained	

Table 13 Revised results generated using all alterations listed in section B with CS (if required) Non-Sjögren's syndrome patients (post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,568	10.11
AT (no ciclosporin)	£15,778	10.05
Difference	£780	0.06
ICER per QALY gained	£13,850 per QALY gained	

Table 14 Revised results generated using all alterations listed in section B with CS (if required) (All patients, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,653	10.10
AT (no ciclosporin)	£15,492	10.07
Difference	£1,161	0.03
ICER per QALY gained	£45,554 per QALY gained	

Table 15: Revised results generated using all alterations listed in section B with CS (if required) (Sjögren's syndrome only, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,530	10.07
AT (no ciclosporin)	£15,689	10.05
Difference	£841	0.02
ICER per QALY gained	£44,874 per QALY gained	

Table 16: Revised results generated using all alterations listed in section B with CS (if required) (non-Sjögren's syndrome only, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,727	10.12
AT (no ciclosporin)	£15,373	10.09
Difference	£1,354	0.03
ICER per QALY gained	£45,814 per QALY gained	

We note that the above cost-effectiveness results do not include adverse events which may occur from the use of corticosteroids[6-8]. Prolonged use of topical corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation[9]. Increase of intraocular pressure may occur even after only a few weeks of treatment[10]. Prolonged use may also suppress the host immune response and thus increase the hazard of secondary ocular infections.

One of the main reasons for using CsA is to reduce the use of long term topical corticosteroids and their potential side effects, including significant glaucoma and cataract formation. Anti-inflammatory treatment is a necessity for patients with severe keratitis and the use of disease-modifying agents are important as an alternative to steroid use {Kolli}. Reduction in the frequency and use of corticosteroids as a result of treatment with Ikervis is likely to lead to secondary savings to the NHS and improvements in patient quality of life through a lessening of the patient and physician burden from the side effects of CS.

Scenario analysis 1: use of alternative stopping rule

The three and six month response rates derived in the SANSIKA study for all patients are reported in the original submission (Table B25) and also in Table 7 above.

Tables 17 to 22 report the ICERs generated as a result of assessing responder status (yes/no) at three rather than six months. Compared to a six month stopping rule, the adoption of a three month stopping rule corresponds to a cost saving of £534 per patient with similar incremental effectiveness. ICERs for Ikervis +AT vs. AT (without ciclosporin) are around £25,000 irrespective of whether or not patients have Sjögren's syndrome.

Due to the lower proportion of responsive patients at month three relative to month six when assessed with the post-hoc definition of response (Table 8), a three month stopping rule is less cost-effective, with ICERs ranging from around £32,000 to around £38,000 per QALY gained.

Table 17 Use of an alternative treatment stopping rule (three rather than six months, All patients, post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,205	9.95
AT (no ciclosporin)	£15,780	9.94
Difference	£425	0.01
ICER per QALY gained	£33,432 per QALY gained	

Table 18 Use of an alternative treatment stopping rule (three rather than six months, Sjögren's syndrome, post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,141	9.93
AT (no ciclosporin)	£15,873	9.92
Difference	£268	0.01
ICER per QALY gained	£38,534 per QALY gained	

Table 19 Use of an alternative treatment stopping rule (three rather than six months, non-Sjögren's syndrome, post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,243	9.97
AT (no ciclosporin)	£15,724	9.95
Difference	£519	0.02
ICER per QALY gained	£32,109 per QALY gained	

Table 20 Use of an alternative treatment stopping rule (three rather than six months, All patients, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,314	9.97
AT (no ciclosporin)	£15,687	9.94
Difference	£627	0.03
ICER per QALY gained	£24,696 per QALY gained	

Table 21 Use of an alternative treatment stopping rule (three rather than six months, Sjögren's syndrome, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,190	9.93
AT (no ciclosporin)	£15,842	9.92
Difference	£348	0.01
ICER per QALY gained	£25,350 per QALY gained	

Table 22 Use of an alternative treatment stopping rule (three rather than six months, non-Sjögren's syndrome, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,388	9.98
AT (no ciclosporin)	£15,594	9.95
Difference	£795	0.03
ICER per QALY gained	£24,529 per QALY gained	

Scenario analysis 2: Use of alternative HRQoL gains

A positive gain in utility was observed for patients who responded to treatment, regardless of treatment regimen or response definition. Due to the highly non-significant effect that treatment regimen (p=0.935) has on the utility gain derived from response (Table 9), it is unreasonable to assume that the observed differences between Ikervis and vehicle in

SANSIKA are anything more than circumstantial. The most appropriate values for decision making purposes are therefore the pooled +0.104 (if using the post-hoc response definition) and the pooled +0.078 (if using the pre-specified response definition).

Full results using the range of utilities reported in the response to clarification questions document can be found in Table 23 and Table 24. With the post-hoc response definition, ICERs spanned from £10,670 to £30,692, and were typically around £15,000 per QALY gained. With the pre-specified response definition, ICERs spanned from £25,786 to £64,617 and were typically around £34,000 per QALY gained.

Table 23 Range of incremental utility benefits in responders compared to non-responders reported in SANSIKA (post-hoc response definition)

Data source	Gain associated with response	ICER per QALY gained
	All patients	
SANSIKA – Pooled[a]	+0.078	£19,463
SANSIKA – NOVA22007[a]	+0.055[b]	£27,451
SANSIKA – Vehicle[a]	+0.104[b]	£14,517
SANSIKA - Pooled[c]	+0.104[b]	£14,517
SANSIKA – NOVA22007[c]	+0.097[b]	£15,565
SANSIKA – Vehicle[c]	+0.135[b]	£11,184
	Sjögren's	
SANSIKA – Pooled[a]	+0.078	£21,761
SANSIKA – NOVA22007[a]	+0.055[b]	£30,692
SANSIKA – Vehicle[a]	+0.104[b]	£16,231
SANSIKA - Pooled[c]	+0.104[b]	£16,231
SANSIKA – NOVA22007[c]	+0.097[b]	£17,403
SANSIKA – Vehicle[c]	+0.135[b]	£12,504
	Non-Sjögren's	
SANSIKA – Pooled[a]	+0.078	£18,569
SANSIKA – NOVA22007[a]	+0.055[b]	£26,190
SANSIKA – Vehicle[a]	+0.104[b]	£13,850
SANSIKA - Pooled[c]	+0.104[b]	£13,850
SANSIKA – NOVA22007[c]	+0.097[b]	£14,850
SANSIKA – Vehicle[c]	+0.135[b]	£10,670

a) pre-specified definition of response; **b)** originally reported in the clarification document as mean attributable difference in utility change; **c)** post-hoc definition of response

Table 24 Range of incremental utility benefits in responders compared to non-responders reported in SANSIKA (pre-specified response definition)

Data source	Gain associated with response	ICER per QALY gained
	All patients	
SANSIKA – Pooled[a]	+0.078	£45,554
SANSIKA – NOVA22007[a]	+0.055[b]	£64,251
SANSIKA – Vehicle[a]	+0.104[b]	£33,979
SANSIKA - Pooled[c]	+0.104[b]	£33,979
SANSIKA – NOVA22007[c]	+0.097[b]	£36,431
SANSIKA – Vehicle[c]	+0.135[b]	£26,176
	Sjögren's	
SANSIKA – Pooled[a]	+0.078	£44,874
SANSIKA – NOVA22007[a]	+0.055[b]	£63,292
SANSIKA – Vehicle[a]	+0.104[b]	£33,472
SANSIKA - Pooled[c]	+0.104[b]	£33,472
SANSIKA – NOVA22007[c]	+0.097[b]	£35,887
SANSIKA – Vehicle[c]	+0.135[b]	£25,786
	Non-Sjögren's	
SANSIKA – Pooled[a]	+0.078	£45,814
SANSIKA – NOVA22007[a]	+0.055[b]	£64,617
SANSIKA – Vehicle[a]	+0.104[b]	£34,173
SANSIKA - Pooled[c]	+0.104[b]	£34,173
SANSIKA – NOVA22007[c]	+0.097[b]	£36,639
SANSIKA – Vehicle[c]	+0.135[b]	£26,326

a) pre-specified definition of response; **b)** originally reported in the clarification document as mean attributable difference in utility change; **c)** post-hoc definition of response

Scenario analysis 3: Exclusion of steroid use

For reasons described in section A of this document, it was not possible to formally undertake an indirect comparison for the efficacy of CsA + CS and AT, and AT + CS) and hence the analysis with the inclusion of CS (if required) is predicated on a number of assumptions. Tables 25 to 30 detail cost-effectiveness results without the inclusion of CS in the analysis.

The ICERs generated using these assumptions range from £13,952 to £16,333 per QALY gained using the post-hoc response definition and from £45,010 to £45,950 with the pre-specified response definition. The omission of steroids from the economic model is unlikely to have a meaningful impact on any reimbursement decision.

Table 25 Revised results generated using all alterations listed in section B without CS – (All patients, post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,301	10.09
AT (no ciclosporin)	£15,587	10.04
Difference	£714	0.05
ICER per QALY gained	£14,619 per QALY gained	

Table 26 Revised results generated using all alterations listed in section B without CS – (Sjögren's syndrome patients, post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,236	10.07
AT (no ciclosporin)	£15,642	10.03
Difference	£594	0.04
ICER per QALY gained	£16,333 per QALY gained	

Table 27 Revised results generated using all alterations listed in section B without CS (Non-Sjögren's syndrome patients, post-hoc response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,340	10.11
AT (no ciclosporin)	£15,554	10.05
Difference	£786	0.06
ICER per QALY gained	£13,952 per QALY gained	

Table 28 Revised results generated using all alterations listed in section B without CS (All patients, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,428	10.10
AT (no ciclosporin)	£15,263	10.07
Difference	£1,165	0.03
ICER per QALY gained	£45,690 per QALY gained	

Table 29: Revised results generated using all alterations listed in section B without CS (Sjögren's syndrome only, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,300	10.07
AT (no ciclosporin)	£15,456	10.05
Difference	£844	0.02
ICER per QALY gained	£45,010 per QALY gained	

Table 30: Revised results generated using all alterations listed in section B without CS (non-Sjögren's syndrome only, pre-specified response definition)

Intervention	Discounted cost	Discounted QALYs
Ikervis + AT	£16,505	10.12
AT (no ciclosporin)	£15,147	10.09
Difference	£1,358	0.03
ICER per QALY gained	£45,950 per QALY gained	

Scenario analysis 4: Cost minimisation analysis versus other ciclosporin formulations

Following the ERGs exploratory cost-minimisation analysis and the committee's restated desire to see a scenario analysis comparing Ikervis to other ciclosporin formulations in section 4.15 of the draft ACD, a simple cost-comparison assuming equivalent efficacy, adverse event profiles and secondary costs of Ikervis to other CsA products used in the UK was performed.

It is noted that for patients with dry eye disease and severe keratitis, different formulations of CsA are used in clinical practice[11] to treat the condition although none are *licensed* for human use in the UK. These include Restasis (0.05% CsA drops) imported from the USA and Optimmune (0.2% CsA ointment) ophthalmic ointment – veterinary product licensed used to treat dry eye in dogs[12].

Using prescribing data from the most recently available version of the Prescription Cost Analysis (PCA) and cost data from the NHS drug tariff, Ikervis is over £150 cheaper per month than Optimmune eye ointment, £382 cheaper than Restasis and almost £300 cheaper than their weighted average.

Table 31 Cost minimisation analysis vs. hospital CsA

Ciclosporin formulation	Monthly cost[a]	Quantity prescribed[b]
Restasis eye drops (0.05%) 0.4ml	£454.20	13,669
Ciclosporin eye ointment, (0.2%)	£227.10	8,427[c]
Ciclosporin eye drops (2%)	-	No longer available
Ciclosporin formulation	**Monthly cost**	**Cost minimisation outcome**
Ikervis	£72.00	Dominant
Hospital ciclosporin (weighted cost)	£367.59	Dominated

a) Sourced from NHS Drug Tariff, July 2015 **b)** Sourced from NHS PCA 2014 **c)** Includes preservative free ointment only

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(9) Allergan. Pred Forte (prednisolone acetate opthalmic suspension, USP) 1% sterile. http://www allergan com/assets/pdf/pred_forte_pi pdf [2013

(10) Becker B. Intraocular pressure response to topical corticosteroids. IOVS 1965;198-205.

(11) Health & Social Care Information Centre. Prescription Cost Analysis, England - 2014 [NS]. http://www hscic gov uk/article/2021/Website-Search?productid=17711&q=prescription+cost+analysis&sort=Relevance&size=10&page=1&area=both#top [2015 Available from: URL:http://www.hscic.gov.uk/article/2021/Website-Search?productid=17711&q=prescription+cost+analysis&sort=Relevance&size=10&page=1&area=both#top

(12) Merck Animal Health. Optimmune Opthalmic Ointment. http://www merck-animal-health-usa com/products/130_163354/productdetails_130_163712 aspx [2015

Appendix 1: Results from stepwise variable selection process (utility analysis)

Table 32 Predictors of change in utility (post-hoc response not included) - backwards data selection

Backwards data selection					
P =0.6681 ≥ 0.2 removing Treatment* Sjögren's					
P =0.7929 ≥ 0.2 removing Ikervis usage					
P =0.5531 ≥ 0.2 removing Sjögren's = yes					
P =0.6681 ≥ 0.2 removing Treatment* Response (pre-specified definition)					
Parameter	**Coefficient**	**s.e.**	**P-value**	**95% LCI**	**95% UCI**
Response (pre-specified definition) = yes	0.072	0.037	0.052	-0.001	0.145
Constant	-.0003	0.020	0.883	-0.043	0.037

Table 33 Predictors of change in utility (post-hoc response not included) - forwards data selection

Forwards data selection					
P =0.0518 ≤ 0.1 adding response (pre-specified definition)= yes					
Parameter	**Coefficient**	**s.e.**	**P-value**	**95% LCI**	**95% UCI**
Response (pre-specified definition) = yes	0.072	0.037	0.052	-0.001	0.145
Constant	-.0003	0.020	0.883	-0.043	0.037

Appendix 2: Statistical output from the piecewise exponential analysis of time to treatment discontinuation

Table 34 Piecewise exponential distribution discontinuation hazard

Treatment regimen	Daily discontinuation hazard	S.E.	Lower 95%	Upper 95%
Ikervis day 0 to day 90	.115%	.030%	.069%	.190%
Ikervis day 90+	.064%	.014%	.042%	.098%
Vehicle day 90+	.068%	.031%	.028%	.164%
Pooled day 0 to day 90	.086%	.020%	.054%	.136%
Pooled day 90+	.065%	.013%	.045%	.095%

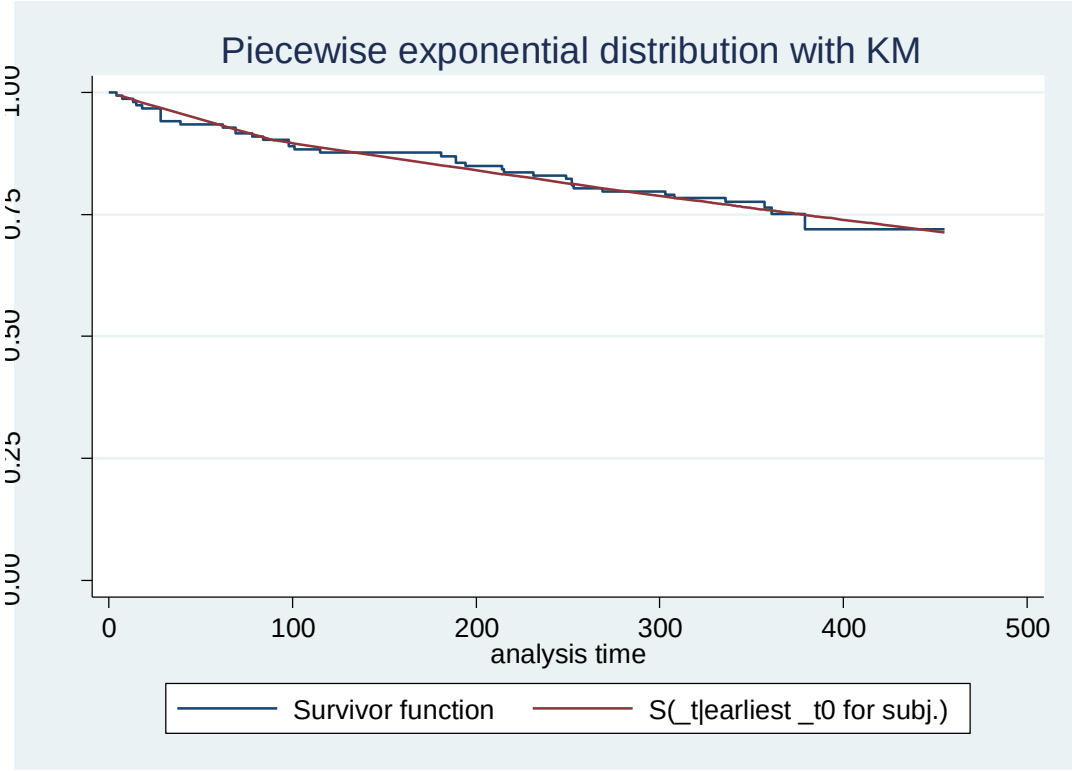


Figure 4 Piecewise exponential distribution (Ikervis only)

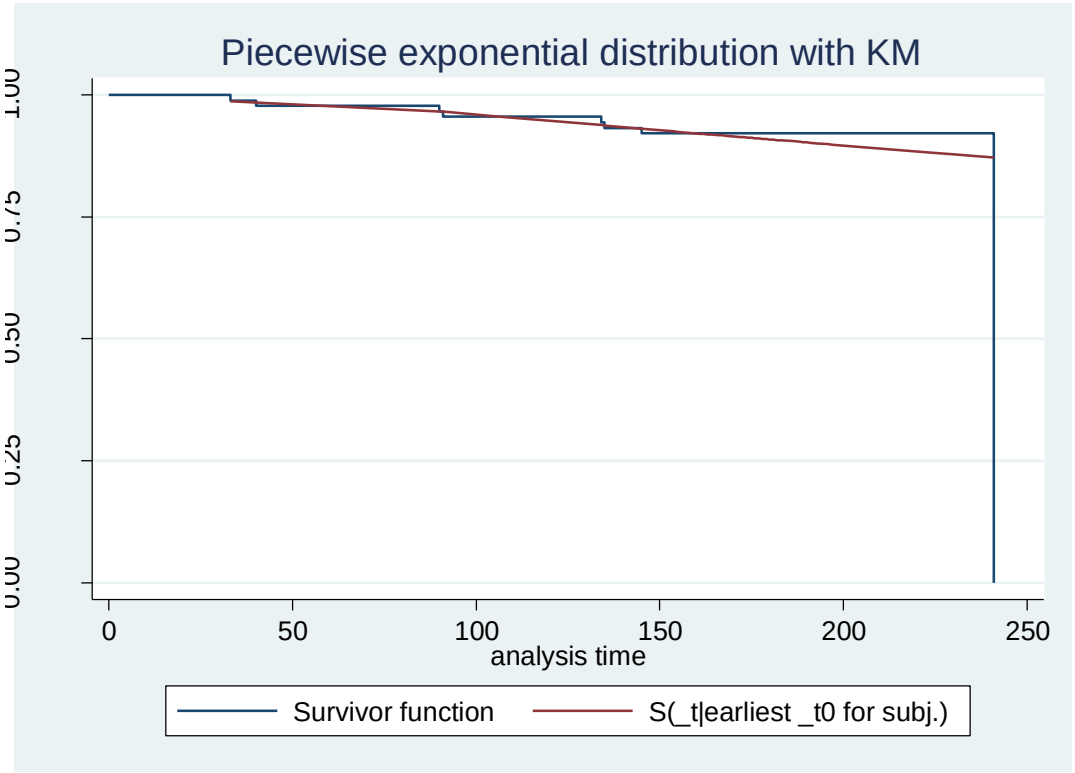


Figure 5 Piecewise exponential distribution (vehicle only)

National Institute for Health and Care Excellence

Ciclosporin for treating dry eye disease which has not improved after treatment with artificial tears [ID665]

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) of Ciclosporin for treating dry eye disease which has not improved after treatment with artificial tears.

The Appraisal Consultation Document was sent to nurses caring for people with dry eye disease to review on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below:

i) **Has the relevant evidence been taken into account?**

Our members suggest that the evidence considered seems comprehensive.

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

Our members consider that the case against has been well made.

iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Our members at this moment in time support the committee's conclusion based on the evidence presented.

Our members commented that they would, however, have liked more detail on the patient's viewpoint. They noted that there are lay members on the appraisal committee, but it is not clear if these lay members are patients. On page 47 it states that patient experts were selected but none were listed as having contributed their personal view on the use of Ciclosporin for treating of dry eye disease. A patient/service user would have added a further perspective.

They also note that the committee has asked NICE to request further analyses from the company, which should be made available for the second Appraisal Committee meeting.

The RCN look forward to receiving the report from the second appraisal committee meeting and would welcome guidance to the NHS on the use of this health technology.

iv) **Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.

Single Technology Appraisal (STA)

Ciclosporin for treating dry eye disease which has not improved after treatment with artificial tears [ID665]

Appraisal consultation document

Professor F C Figueiredo (FF) Comments on ACD above
17th July 2015

As per NICE request the Appraisal Committee is interested in receiving comments on the following questions (**in RED**):

- ***Has all of the relevant evidence been taken into account?***

FF Comments: It is rather important to take into consideration the seriousness of severe dry eye disease (DED) associated with keratitis (i.e. significant impact on patient's QoL and high risk of serious ocular surface infection if left untreated) where IKERVIS has clearly demonstrated a significant benefit (i.e. improvement of keratitis).

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

FF comments:

Page 12:
Patients with temporary or permanent punctal plugs were assumed to not use artificial tears.

Comment [n1]: This is an incorrect concept.

Page 16:
The ERG stated that it is unclear whether CFS-OSDI response is a clinically relevant end point

Comment [n2]: It is indeed relevant

Page 17:
The ERG considered that there was no sufficient evidence available to support a cost-effectiveness analysis of ciclosporin compared with established clinical practice in the NHS for severe dry eye disease

Comment [n3]: The main point here is the significant improvement of keratitis and HLA expression in patients with severe dry eye associated with keratitis. This is a high risk group of patients given their serious vulnerability to develop secondary ocular surface infection and the impaired QoL given high symptomatology and poor sight.

Page 22:
The Committee also understood that in clinical practice ciclosporin would be given in combination with corticosteroids (if needed) and artificial tears, and concluded that this represents established clinical practice without ciclosporin, that is, the definition of the comparator in the final NICE scope.

Comment [n4]: Not necessarily?

Page 23
Optimmune ointment is more widely used in the NHS for people with severe dry eye disease but that many people are not willing to have treatment because of its veterinary marketing authorisation. The clinical experts also noted that it can only be used at night because it causes blurred vision and that there are some people who cannot tolerate ointments.

Comment [n5]: Not entirely true

Page 25:

The clinical experts also stated that people with severe dry eye disease are close to having complete corneal blindness

Comment [n6]: This is not necessarily true. It is an extremely rare event/complication of DED.

Page 26:

However, it was aware that the ERG considered that the clinical relevance of this revised definition of response was unclear and that it excluded the level of benefit which most favoured the vehicle group.

Comment [n7]: The indication for IKERVIS use is very specific as per company's proposal. This is rather important to tackle the more severe and most difficult patients with a more sever degree of dry eye disease associated with significant keratitis.

The clinical experts stated that in clinical practice there is no clear definition for response and non-response, but that the greater the benefit in CFS the more likely this would have a beneficial effect in slowing disease progression.

Comment [n8]: Often associated with improvement of symptoms that is highly important that would consequently improve patient's QoL.

The Committee had reservations about all the post hoc analyses presented by the company and considered that these analyses were not robust enough to reach a conclusion on the relative clinical effectiveness of ciclosporin compared with the vehicle.

Comment [n9]: In my view the pos hoc analysis is rather important as it showed a significant improvement of keratitis associated with dry eye disease. This is highly relevant given the risk of secondary infection associated with keratitis in patients with dry eye. All dry ye patients are more vulnerable to ocular surface infection in particular to bacterial keratitis due to a decreased ocular surface protection provided by a normal tear film.

Page 27:

Committee concluded that the company's model was of limited relevance because it failed to show the cost effectiveness of ciclosporin compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears.

Comment [n10]: It is rather important to highlight that our most recent day-to-day management experience in clinical practice has been influenced by the post-RESTASIS usage in patients with dry eye in other parts of the world where RESTAIS is available and the design of the SANSIKA study was to use a single treatment in addition to artificial tears for the management of DED that has proved to be more effective in patients with severe DED associated with significant keratitis.

The Committee heard from the clinical experts that in clinical practice treatment is not stopped because of adverse effects.

Comment [n11]: This is not necessarily correct as patients do stop treatment in the presence of side effect, however we do try to persuade patients to persevere with topical treatment in the assumption that the local side effect will improve with time or completely resolve. Local AEs are largely thought to be transient in DED and have a very limited impact on patient's QoL.

Page 29:

The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life

The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life.

Comment [n12]: There is no evidence of a log term-effect of cyclosporin adverse event on patient QoL

Page 37:

The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life.

Comment [n13]: As previously reported most topical side effect are transitory and of no long-term importance.

The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice.

Comment [n14]: There is no hard/published evidence regarding a uniform established clinical practice. Therefore, it would be erroneous and possibly inappropriate to expect that we do have uniform and well established clinical practice for the management of patients with severe dry eye associate with severe keratitis.

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

FF comments:

Unlicensed cyclosporin A is routinely used in NHS ocular surface clinics across the UK. A failure to support IKERVIS use in the NHS despite EMA MA will maintain a system of continued use of unlicensed cyclosporin A in the UK that is unjustifiable given the fact that the rest of the world is using a licensed cyclosporin A compound regularly to treat patients with dry eye disease.

19th July 2015,

Professor Francisco C Figueiredo, MD, PhD, FRCOphth

Name	[redacted]
Organisation	UK Ophthalmic Pharmacy Group
Role	NHS Professional
Job title	[redacted]
Location	England
Conflict	No
Disclosure	«Disclosure»
Comments	«Comment_Id» 670 «Comment_type» General Dry eye disease - ciclosporin (after artificial tears): appraisal consultation National Institute for Health and Care Excellence Eyes and vision The UK Ophthalmic Pharmacy Group's comments, endorsed by the Royal Pharmaceutical Society are as follows: Topical ocular ciclosporin has been used in ophthalmology for many years for a wide range of indications including the licensed use for IkervisÂ® â€˜Treatment of severe keratitis in adult patients with dry eye disease which has not improved despite treatment with tear substitutesâ€™. There is a wealth of evidence to support the use of topical ciclosporin in addition to the SANSIKA and SICCANOVE trials which relate specifically to the IkervisÂ® product (see attached prepared by Edward Hindle, 2014) Initially an unlicensed preparation containing ciclosporin 2% in arachis oil manufactured by Moorfields Pharmaceuticals was used but as this was poorly tolerated, many prescribers turned to the veterinary product OptimmuneÂ® eye ointment containing ciclosporin 0.2% and then when Allerganâ€™s RestasisÂ®, single dose eye drops containing ciclosporin ophthalmic emulsion 0.05% became available in the USA, this was imported via a pharmaceutical wholesaler. Moorfields Pharmaceuticals then produced a multidose preservative-free formulation of ciclosporin 0.06% until the unit closed last year. All these products, due to their wide use were or are included in the Drug Tariffâ€™s list Part VIIIB - Arrangements for payment for Specials and Imported Unlicensed Medicines Ciclosporin 2% eye drops (Moorfields Pharmaceuticals) from November 2012 to May 2015; last price @ May 2015 Â£126.53 for 10ml Ciclosporin 0.2% eye ointment from November 2012 to date; current price Â£80.69 for 3.5g

	Ciclosporin 0.05% unit dose eye drops (RestasisÂ®, imported) from November 14 to date; current price Â£7.57 for each 0.4ml unit. With a licensed frequency of one drop every 12 hours this equates to Â£454.20 for 30 daysâ€™ treatment. Ciclosporin 0.06% multidose eye drops (Moorfields Pharmaceuticals) from November 14 to May 15 (last price @ May 2015 Â£53.03 for 10ml). There is no standard in use shelf life for multidose preservative-free eye drops so with some pharmacies allocating 24 hours shelf life and others 7 daysâ€™ shelf life this equates to Â£212 to Â£1,484.84 for 28 daysâ€™ treatment. Members of the UK Ophthalmic Pharmacy Group were delighted to hear that Santen are to bring a licensed topical ophthalmic preparation of ciclosporin to the market. Many Hospital Trustsâ€™ formularies contain one or both preparations of ophthalmic ciclosporin purchased as unlicensed products and we look forward to using the licensed preparation for both the licensed indication and the many as yet unlicensed indications for the product instead of the unlicensed product in accordance with the MHRAâ€™s guidance, the General Medical Councilâ€™s guidance and the Royal Pharmaceutical Societyâ€™s guidance on use of unlicensed preparations. With the forthcoming launch of IkervisÂ®, we expect Trust Drug & Therapeutics Committees/Medicines Management Committees to restrict the prescribing of IkervisÂ® in the hospitals, possibly to consultant ophthalmologists specialising in corneal diseases, and Area Prescribing Committees restricting to continuation of therapy by General Practitioners following specialist initiation. Thus, we expect prescribing of IkervisÂ® to be strictly limited and would support this approach to enable ophthalmic pharmacists to supply a licensed product rather than the very costly unlicensed products currently in use. We support the statement in the attached summary updated in view of the impending launch of a licensed product â€˜The licensed ciclosporin product should be available to patients who have been assessed by an appropriate specialist and this should be available to be continued in primary careâ€™. [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] UK Ophthalmic Pharmacy Group July 15 We have a pdf document reviewing ocular uses of ciclosporin to accompany comment 1 - please advise how to submit this?
Submission date	2015 07 15

Name	[redacted]
Organisation	College of Optometrists

Role	Professional body for optometrists
Job title	[redacted]
Location	England
Conflict	No
Disclosure	«Disclosure»
Comments	«Comment_Id»671 «Comment_type» We are of the opinion that the recommendations are not discriminatory against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. We wanted to raise our concern regarding the definitions of Dry Eye Disease (DED) that were used in the two studies considered. They were based on a combination of clinical features and symptoms, for which there is indeed a well-established precedent. However in DED there is a notorious lack of correlation between signs and symptoms (a fact which is acknowledged in the document). In addition, it is not apparent in either study that the type of DED had been characterised. DED is divided into aqueous-deficient and evaporative types, and the two types have different pathogenic mechanisms. (Confusingly however, the two types may co-exist.) In that the SICCANOVE study included a measurement of tear break-up time, the possibility of evaporative DED was recognised, but this does not appear to apply to the inclusion criteria of the SANSIKA study. The provisional recommendations are sound and are a suitable basis for guidance to the NHS. Further evidence on the efficacy and cost-effectiveness of ciclosporin in the management of severe dry eye is required before this medicine can be recommended within the NHS. We are aware that ciclosporin for ophthalmic use is not currently available in the UK and its use is not recommended in any guidance published by the College of Optometrists. We agree that all of the relevant evidence has been taken into account. The findings of the NICE evidence synthesis review are consistent with a recently published systematic review by Saccheti et al http://www.ncbi.nlm.nih.gov/pubmed/24344232 We have considerable experience of the use of Optimmune ointment in severe chronic allergic eye disease (i.e. Vernal and Atopic Keratoconjunctivitis). Experience suggests that very few patients are alarmed by the prospect of using a veterinary product if the reasons for its prescription are carefully explained by the clinician. The real problem comes with the continuation

	of supplies when the GP refuses to prescribe a veterinary product because it is not on the list of prescribable drugs. Ointment does cause some blurring of vision - perhaps for 20 minutes or so - and this is generally well tolerated by patients who appreciate that the benefits of treatment outweigh the transitory side-effects. It is true that ointment base (which contains lanolin) is not tolerated by a very small proportion of patients. We are of the opinion that this paragraph may dismiss or at any rate discourage the possibility of using a very important source of topical ciclosporin, namely Optimmune ointment. We agree that the summary of clinical effectiveness is reasonable interpretations of the evidence. We agree that the summary of cost effectiveness is reasonable interpretations of the evidence.
Submission date	2015 07 15

Name	[redacted]
Organisation	International Glaucoma Association
Role	[redacted]
Job title	[redacted]
Location	England
Conflict	No
Disclosure	«Disclosure»
Comments	«Comment_Id»672 «Comment_type» General The International Glaucoma Association, as representative of many glaucoma patients where dry eye is not uncommon, is concerned now Ikervis is a licensed product, the un-licensed ciclosporin drops will be withdrawn and leave the prescriber and the patients with no like for like alternative to control their dry eye. As the un-licensed ciclosporin drops have been 'a last alternative' to gain relief for many patients this would be a regrettable situation. We trust the consultation committee will take this into consideration when making their judgement.
Submission date	2015 07 15

Dry eye disease - ciclosporin (after artificial tears): appraisal consultation
National Institute for Health and Care Excellence
Eyes and vision

The UK Ophthalmic Pharmacy Group's comments, endorsed by the Royal Pharmaceutical Society are as follows:

Topical ocular ciclosporin has been used in ophthalmology for many years for a wide range of indications including the licensed use for Ikervis® 'Treatment of severe keratitis in adult patients with dry eye disease which has not improved despite treatment with tear substitutes'. There is a wealth of evidence to support the use of topical ciclosporin in addition to the SANSIKA and SICCANOVE trials which relate specifically to the Ikervis® product (see attached prepared by Edward Hindle, 2014)

Initially an unlicensed preparation containing ciclosporin 2% in arachis oil manufactured by Moorfields Pharmaceuticals was used but as this was poorly tolerated, many prescribers turned to the veterinary product Optimmune® eye ointment containing ciclosporin 0.2% and then when Allergan's Restasis®, single dose eye drops containing ciclosporin ophthalmic emulsion 0.05% became available in the USA, this was imported via a pharmaceutical wholesaler.

Moorfields Pharmaceuticals then produced a multidose preservative-free formulation of ciclosporin 0.06% until the unit closed last year. All these products, due to their wide use were or are included in the Drug Tariff's list
Part VIIIB - Arrangements for payment for Specials and Imported Unlicensed Medicines

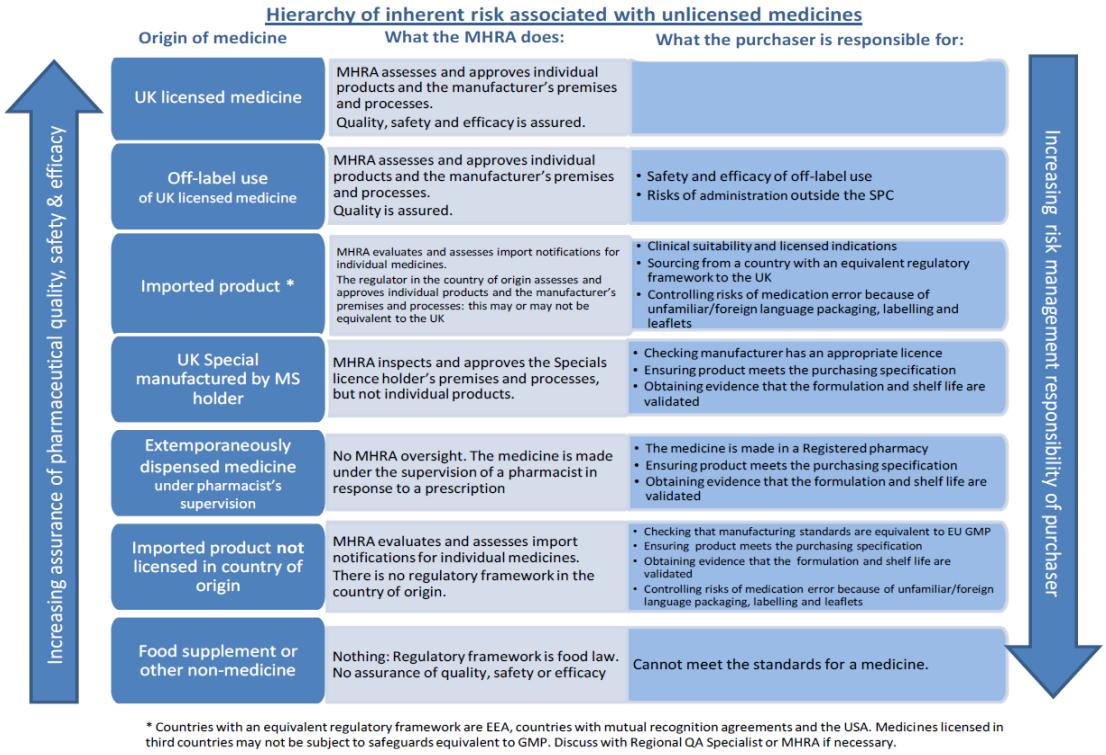
Ciclosporin 2% eye drops (Moorfields Pharmaceuticals) from November 2012 to May 2015; last price @ May 2015 £126.53 for 10ml

Ciclosporin 0.2% eye ointment from November 2012 to date; current price £80.69 for 3.5g

Ciclosporin 0.05% unit dose eye drops (Restasis®, imported) from November 14 to date; current price £7.57 for each 0.4ml unit. With a licensed frequency of one drop every 12 hours this equates to £454.20 for 30 days' treatment.

Ciclosporin 0.06% multidose eye drops (Moorfields Pharmaceuticals) from November 14 to May 15 (last price @ May 2015 £53.03 for 10ml). There is no standard in use shelf life for multidose preservative-free eye drops so with some pharmacies allocating 24 hours shelf life and others 7 days' shelf life this equates to £212 to £1,484.84 for 28 days' treatment.

Members of the UK Ophthalmic Pharmacy Group were delighted to hear that Santen are to bring a licensed topical ophthalmic preparation of ciclosporin to the market. Many Hospital Trusts' formularies contain one or both preparations of ophthalmic ciclosporin purchased as unlicensed products and we look forward to using the licensed preparation for both the licensed indication and the many as yet unlicensed indications for the product instead of the unlicensed product in accordance with the MHRA's guidance, the General Medical Council's guidance and the Royal Pharmaceutical Society's guidance on use of unlicensed preparations.



With the forthcoming launch of Ikervis®, we expect Trust Drug & Therapeutics Committees/Medicines Management Committees to restrict the prescribing of Ikervis® in the hospitals, possibly to consultant ophthalmologists specialising in corneal diseases, and Area Prescribing Committees restricting to continuation of therapy by General Practitioners following specialist initiation. Thus, we expect prescribing of Ikervis® to be strictly limited and would support this approach to enable ophthalmic pharmacists to supply a licensed product rather than the very costly unlicensed products currently in use.

We support the statement in the attached summary updated in view of the impending launch of a licensed product 'The licensed ciclosporin product should be available to patients who have been assessed by an appropriate specialist and this should be available to be continued in primary care'.

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted]
On behalf of the UK Ophthalmic Pharmacy Group
July 2015

We also have a pdf attachment to accompany these comments

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ciclosporin for treating dry eye disease

ERG report for second Appraisal Committee meeting

This report was commissioned by the NIHR HTA Programme as project number 13/106/01

Completed 7 August 2015
Minor corrections 28 August 2015

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The Appraisal Committee requested that the following additional work be undertaken by the company for consideration at the second Appraisal Committee meeting:

- An indirect treatment comparison of the clinical effectiveness of ciclosporin (CsA) plus corticosteroids (CS) (if needed) and artificial tears (AT), and that of CS (if needed) and AT
- An economic model comparing the cost effectiveness of CsA + CS (if needed) and AT, with that of CS (if needed) and AT. This cost effectiveness analysis should include:
    - the original SANSIKA Corneal Fluorescein Staining – Ocular Surface Disease Index (CFS-OSDI) definition of response (that is, improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI)
    - an evidence based treatment stopping rates with CsA + CS (if needed) and AT
    - changes to resource use and costs reflecting:
        - that AT may be used alongside punctal plugs
        - both a baseline average and a 6 month average for the number of artificial tear drops used per day, for both treatment groups
        - the assumption that CsA is dispensed and costs are incurred monthly
        - sensitivity analyses using different utility values for response by treatment group
    - A subgroup analysis for people with Sjögren's syndrome (SS) and severe dry eye disease (DED).

The company presented a 27 page document with new evidence alongside an updated systematic review report[1] and a modified model provided in Microsoft Excel. This document presents a summary and critique of the company's new evidence by the Evidence Review Group (ERG).

2 ORIGINAL SCOPE AND DECISION PROBLEM

Table 1 displays the original scope for this submission and the decision problem addressed by the company's original submission.

Table 1 NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company's submission
Population	People with severe dry eye disease (DEWS 3 or 4) whose disease has not adequately responded to tear substitutes	Patients with DED and severe keratitis which has not improved despite treatment with tear substitutes
Intervention	Ciclosporin	Ciclosporin*
Comparator(s)	Standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments, and acute use of topical corticosteroids)	Standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments, and acute use of topical corticosteroids)†
Outcomes	The outcome measures to be considered include: • Eye pain and discomfort • Symptoms of dry eye disease including: photosensitivity; ability to open eyes; visual acuity; ability to concentrate • Adverse effects of treatment • Health-related quality of life	Signs and symptoms (composite outcome): • CFS-OSDI responder Signs: • CFS using modified Oxford scale • Inflammation (HLA-DR) • Tear film osmolarity • TBUT Symptoms: • OSDI • Ocular discomfort (using VAS) • Other symptoms (by a VAS): burning; stinging; foreign body sensation; itching; eye dryness; pain; blurred vision or sticky feeling; photophobia Adverse effects of treatment Health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	The economic analysis follows the NICE reference case and the cost effectiveness of Ikervis is expressed in terms of incremental cost per quality-adjusted life year A lifetime horizon has been used to estimate both clinical and cost effectiveness and reflects the potential differences in costs and outcomes between the technologies compared Costs have been considered from an NHS and Personal Social Services perspective
Subgroups to be considered	If the evidence allows, a subgroup analysis of people with Sjögren's syndrome should be considered	None

CFS=Corneal staining; DED=dry eye disease; DEWS=Dry Eye Workshop; HLA-DR=Human leukocyte antigens DR; OSDI=Oxford Surface Disease Index; TBUT=Tear film break up time; VAS=visual analogue scale
* The ERG notes that the exact intervention was the formulation of ciclosporin known as Ikervis as opposed to any ciclosporin formulation
† Trial evidence is actually only presented from Ikervis vehicle which contain different excipients in each trial whereas cost-effectiveness evidence assumes vehicle to be the same as AT
Source: Table 2 of original ERG report[2]

3 SUMMARY AND CRITIQUE OF NEW CLINICAL EFFECTIVENESS EVIDENCE

3.1 Trials identified by the company

From an updated systematic review of the literature (May 2015), the company presented new clinical evidence from indirect treatment comparisons of three trials,[3-5] including SANSIKA[4] from which the majority of evidence in its initial submission was derived. The ERG has summarised the characteristics of these trials in Table 2.

It is reiterated by the ERG that the pivotal trial in the company's original submission was SANSIKA.[4] This is the only trial which evaluated the effectiveness of the licensed formulation of CsA (Ikervs® at a dose of 1 mg/mL [0.1% CsA]).

In addition, the ERG notes that trials[3-5] were heterogeneous in terms of study populations, length of follow-up and outcomes measured. In particular, Lin and Gong 2015[5] only included patients with SS, who on average were younger and were assessed by a different scale for measuring CFS (a 4-point scale) than in the other two studies[3,4] (which used the 5-point Oxford or modified Oxford scales) and presented findings for differences between arms at different time points, as opposed to changes over time between arms. Furthermore, in Lin and Gong 2015,[5] patients were asked to abstain from the concomitant use of any other ophthalmic drugs, topical CS, or punctal plugs. Investigators in SANSIKA[4] also precluded the use of topical CS but patients were permitted to use concomitant AT (provided by the company) if required and prior punctal plugs were allowed. SANSIKA[4] was the only trial that included patients in which all patients had DED with severe keratitis (37.6% also had SS). It is unclear if these medications were permitted by Jee et al 2014,[3] this trial allowed the inclusion of patients with moderate to severe DED (proportion of patients with SS not reported). Importantly, in terms of the link between evidence for clinical effectiveness and cost effectiveness, SANSIKA[4] is the only trial which measured effectiveness using the composite CFS-OSDI response endpoint.

Table 2 ERG summary of trial characteristics of studies identified for inclusion in the indirect treatment comparison considered by the company

Trial	RCT details (number randomised)	Population (location)	Intervention (number analysed) [Mean (SD) age of subjects]	Comparator (number analysed) [Mean (SD) age of subjects]	Outcomes
SANSIKA[4]	Double-blind: 24 weeks (n=261)	DED patients with severe keratitis (Europe, including UK)	CsA (Ikervis 0.1%) + AT (n=154) [Age: 60.8 (13.5)]	Vehicle (CKC) + AT (n=91)* [Age: 62.1 (11.8)]	Primary: composite CFS-OSDI response at 6 months† Secondary: change in CFS score; complete corneal clearing; % responders based on CFS; change in Schirmer's test score without anaesthesia; change in lissamine green staining score; change in tear film break up time (TBUT); impression cytology for conjunctival cell surface human leukocyte antigen-DR (HLA-DR) expression; tear film osmolarity; change in OSDI score; % responders based on OSDI; change in global ocular discomfort (VAS); % of responders based on improvement in ocular symptoms (VAS); artificial tear use; investigator global evaluation of efficacy; health-related quality of life; safety (AEs and tolerability)
Lin and Gong 2015[5]	Open-label: 8 weeks (n=40)	Patients with SS (China)	CS (fluorometholone 0.1%) + AT (sodium hyaluronate 0.1%) (n=19) [Age: 50.42 (10.85)]	CsA (0.5%) [hospital formulated] + AT (sodium hyaluronate 0.1%) (n=16) [Age: 49.94 (10.74)]	Primary (measured at 2, 4 and 8 weeks): CFS; OSDI; conjunctival goblet cell density; severity of conjunctival congestion Secondary (measured at 2, 4 and 8 weeks): TBUT; Schirmer's test score AEs and tolerability
Jee et al 2014[3]	Double-blind: 13 weeks (n=100)	Patients with moderate to severe DED (South Korea)	Preservative free AT (sodium hyaluronate 0.1%) + CS (fluorometholone 0.1%) followed by CsA (Restasis 0.05%) + preservative free AT (sodium hyaluronate) (0.1%)§ (n=50)¥ [Age: 59.26 (6.32)]	Preserved AT (sodium hyaluronate 0.1%) + CS (fluorometholone 0.1%) followed by CsA (Restasis 0.05%) + preserved AT (sodium hyaluronate) (0.1%)§ (n=50)¥ [Age: 56.75 (5.79)]	Change over time between arms for: OSDI; CFS; TBUT; Schirmer's test score; impression cytology; goblet cell density; antioxidant and inflammatory cytokine activities in tears No distinction was made between primary and secondary outcomes

AEs=adverse events; AT=artificial tears; CFS=corneal fluorescein staining; CKC=cetalkonium chloride; DED=dry eye disease; OSDI=Ocular Surface Disease Index; RCT=randomised controlled trial; SD=standard deviation; SS=Sjögren's syndrome; TBUT=tear film break up time

* 90 patients included in safety analysis

† Improvement of ≥ 2 points from baseline in CFS based on the modified Oxford scale and improvement by ≥ 30% from baseline in OSDI

§ Initial treatment with no CsA was for one month and treatment with CsA for two months

¥ 50 patients were included in the analysis of baseline characteristics but patients withdrew from the study over time (reasons given in paper); it is unclear if all 50 were included in the final analyses

3.2 Findings from individual trials

A summary of the findings and the ERG's critique of SANSIKA[4] appeared in the original ERG report.[2] For the two additional studies[3,5] identified by the company, the ERG makes the following observations:

1. With the exception of Schirmer's test score, Lin and Gong 2015[5] reported an improvement over time for all outcomes with both CsA and CS. Compared with CsA, mean CFS was statistically significantly lower with CS after 2 weeks (P=0.042) but not at 4 or 8 weeks, OSDI was statistically significantly lower with CS at week 4 (P=0.042) but not at 2 or 8 weeks, conjunctival congestion was statistically significantly less at week 4 with CS (P=0.035) but not at 2 or 8 weeks, TBUT was statistically significantly longer after 8 weeks with CS (P=0.04) but not at 2 or 4 weeks. There were no instances of moderate-to-severe transient burning sensation (Grade 2 or 3) upon instillation of CS, unlike with CsA (31.25% at week 2, 12.50% at week 4 and 12.50% at week 8); in SANSIKA[4] site pain was reported by 30.5% of patients treated with CsA (Ikervis). However, it should be noted that the systematic review report[1] commissioned by the company found the Lin and Gong 2015[5] study to be at high risk of bias in terms of patient dropout rates (20% in the CsA arm and 5% in the CS arm). Furthermore, the Lin and Gong 2015[5] study is arguably of limited relevance due to the short follow-up period of patients (8 weeks), presumably necessitated by the fact that it is generally considered by clinicians that CS can only be given for a maximum of 8 weeks. Lin and Gong 2015[5] propose that patients with SS should initially be treated with CS "to rapidly control inflammation and that CsA should be used afterward as a consolidation therapy." However, the ERG notes that clinicians present at the first Appraisal Committee meeting stated they would usually offer CS *with* CsA for the first 8 weeks of treatment. The ERG further notes that the relevance of the study findings to the current appraisal may be questioned given the CsA formulation in this study was a hospital formulated CsA (0.5%) and not Ikervis (0.1%).
2. In Jee et al 2014,[3] compared to treatment with preserved eye drops, treatment with preservative-free eye drops led to statistically significant improvements in OSDI (P<0.05 at both 2 and 3 months), CFS (P<0.05 at 1, 2 and 3 months), TBUT (P<0.05 at both 2 and 3 months), Schirmer's test score (P<0.05 at 1, 2 and 3 months), impression cytologic findings (P<0.05 at both 2 and 3 months) and globlet cell density (P<0.05 at both 2 and 3 months). Reports of "stinging eyes" requiring patients to withdraw from the study were also fewer with preservative-free eye drops (6% vs 10%) than with preserved eye drops. Although the CsA formulation in this study was

Restasis (0.5%) and not Ikervis (0.1%), these findings could arguably be interpreted to present supportive evidence for the use of preservative-free eye drops over preserved eye drops, as proposed by the company for Ikervis (with the preservative free, cetalkonium chloride, as the vehicle).

3.3 Indirect treatment comparison(s)

The company considered three possible approaches to conducting the requested indirect treatment comparison:

1. Dose equivalence between CsA doses
2. Connection via fluorometholone (CS)
3. Connection via fluorometholone (CS) and vehicle.

The first two approaches enabled the possible inclusion of all three trials[3-5] whereas the third approach only enabled the possible inclusion of SANSIKA[4] and Lin and Gong 2015.[5] In relation to each of these approaches, the company stated:

1. Pre-clinical studies conducted by the company indicate that there is improved bioavailability with CsA 1 mg/mL versus lower doses of CsA (Restasis® 0.05% CsA) and European Medicines Agency (EMA) approval[6] was only provided to Ikervis® (0.1% CsA). It was therefore considered inappropriate to pool the doses of CsA and so an indirect treatment comparison could not be undertaken of CsA with the comparators (vehicle or CS, both either with or without AT)
2. Since SANSIKA[4] (and, the ERG notes, Lin and Gong 2015[5]) precluded the use of CS with CsA, it was considered inappropriate to pool "CsA alone" (or CsA + AT) with "CsA + corticosteroids" (or CsA + CS + AT) and therefore an indirect treatment comparison could not be undertaken since a connection with the pivotal SANSIKA[4] trial could not be made
3. As stated in the draft Appraisal Consultation Document (ACD) document (section 4.4) vehicle is considered comparable with the AT Cationorm® which does not include any active agents. It was therefore not thought appropriate to assume vehicle + AT and CS + AT to be equivalent and to pool data from these arms. Therefore, an indirect treatment comparison could not be conducted by the company. The ERG notes that if it is assumed vehicle + AT and CS + AT are equivalent comparators, this approach proposed by the company would only enable a comparison of Ikervis (0.1% CsA) to Restasis (0.05% CsA) which was not a comparison requested by the Appraisal Committee.

In addition to the company's reasons for not conducting an indirect treatment comparison, the ERG considers an indirect treatment comparison would be inappropriate because the trials are heterogeneous in terms of their characteristics and, importantly, in terms of outcomes measured, as described above and summarised in Table 2. Thus in conclusion, the ERG concurs with the company that it is not possible to undertake a robust indirect treatment comparison.

4 SUMMARY AND CRITIQUE OF NEW COST EFFECTIVENESS EVIDENCE

The company has provided a revised decision model in which all of the specific issues indicated in the Appraisal Consultation Document (ACD) have been addressed. These are summarised in Table 3, together with the ERG's assessment of each of the changes made.

Table 3 Summary of changes made to the economic model in response to ACD requests

Amendment requested in ACD	Company changes to economic model	ERG comment
Model to include cost of CS in both arms of the model	Cost of CS added to Ikervis arm to match comparator arm	Amendment confirmed; applied in revised analysis
Model to include use of original trial definition* of response to treatment	This facility already existed in the model originally submitted. No change to model structure required	Pre-specified definition of response used in revised analysis
Inclusion of evidence based treatment stopping rates	Regression-based time-on-treatment models from SANSIKA[4] data applied to model treatment costs in both arms Parallel Markov models included in the model assuming trial treatment stops at 3 months	Amendments confirmed, and applied in revised analysis
AT use alongside punctal plugs	Cost of AT use included in cost of punctal plugs	Amendment confirmed; applied in revised analysis
Common baseline and 6 month average use of ATs for both arms	Parameter values have been revised using trial data	Amendment confirmed; applied in revised analysis
Assume CsA is dispensed and costed monthly	Costs modified using a mid-cycle average number of patients on treatment	This method is not accurate. ERG monthly method gives larger incremental cost and ICER
Treatment-specific utility values for response to treatment	Trial-based treatment-specific response utility parameters calculated	Amendment confirmed, but **not** used in revised analysis
Subgroup analysis by SS / non-SS patients	Logistic regression used to estimate response rates for patients with/without SS	Amendment confirmed; used in revised analysis

ACD=Appraisal Consultation Document; AT=artificial tears; CS=corticosteroids; CsA=ciclosporin; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; SS=Sjögren's syndrome

* Original trial definition was an improvement of ≥ 2 points from baseline in corneal fluorescein staining (CFS) based on the modified Oxford scale and improvement by ≥ 30% from baseline in Ocular Surface Disease Index (OSDI) whereas the company's original base-case had used a post-hoc definition defined as an improvement of ≥ 3 points from baseline in CFS based on the modified Oxford scale and improvement by ≥ 30% from baseline in OSDI

4.1 Utility change related to response to treatment

It is noteworthy that the only requested change which the company did not include in their revised base case analysis concerns the use of treatment-specific utility values for response to treatment.

The company presents results of a step-wise regression analysis to support their view that there is no justification for applying differential values to the utility gain according to the treatment received in the SANSIKA[4] trial. At first sight this appears to be a convincing argument in favour of their contention that utility results from the two trial arms should be pooled.

However, closer examination reveals that there is a systematic imbalance in the condition of responding patients (measured in terms of mean EQ-5D utility score) at the beginning of the SANSIKA[4] trial as shown in Figures 1 and 2 (and also summarised in Appendix). In addition it can be seen that the health-related quality of life benefit gained from a confirmed response to treatment is substantially greater in the vehicle arm of the SANSIKA[4] trial than in the intervention arm (1.9 times when the original trial definition of response is considered and 1.4 times with the post-hoc definition). It is also noticeable that the utility gain and the baseline utility value appear to increase in step. This raises the possibility that the inclusion of this item, and perhaps other variables, into the company's regression analysis may have led to quite different results. In any case, it is clear that by pooling the two trial arms and assigning the same overall average utility gain to both treatments there is a risk of introducing a serious bias into the cost effectiveness analysis; this understates the utility gain recorded in the comparator arm of the trial and overstates the gain in the intervention arm.

The extent of this bias is evident in the results obtained from the new version of the company model (Tables 4 and 5), which show that the choice between separate and pooled utility gain estimates makes the difference between obtaining quantifiable incremental cost effectiveness ratios (ICERs), and Ikervis being dominated by the comparator (less effective and more costly). Clearly this is the most important issue influencing the estimation of cost effectiveness in this appraisal.

Page superseded – please see erratum

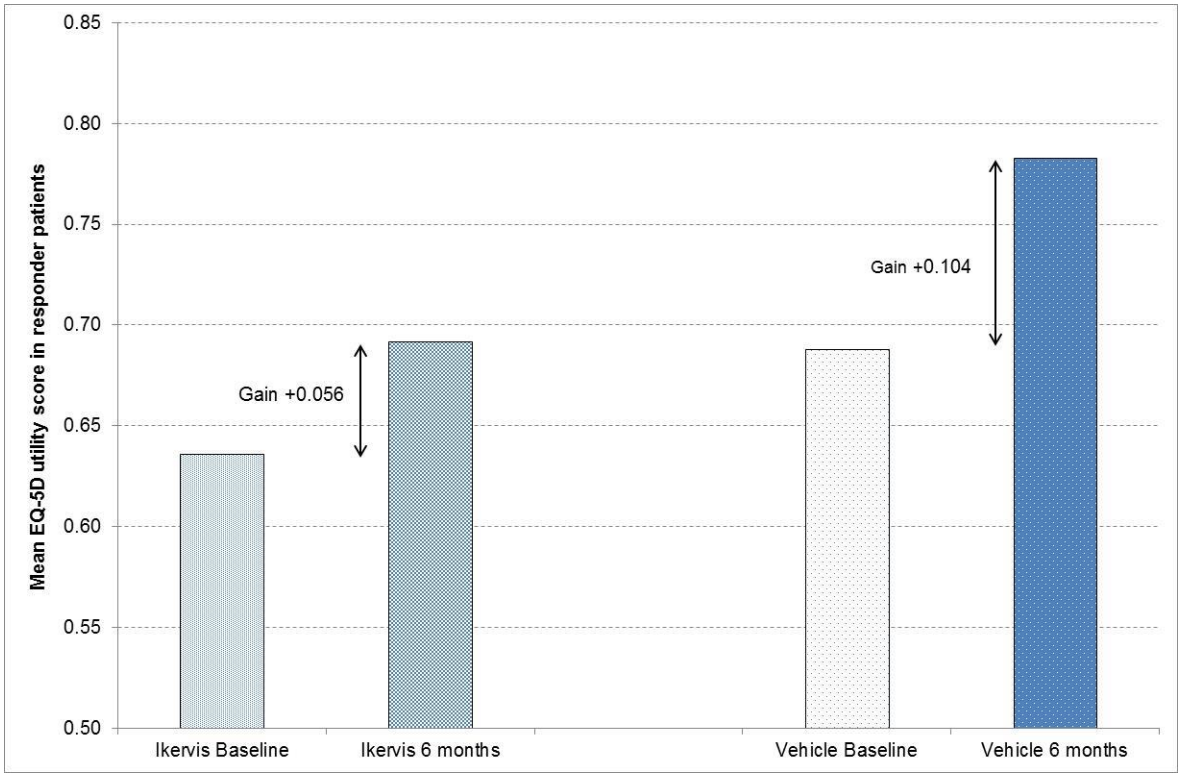


Figure 1 Comparison of utility gain associated with response to treatment for Ikervis and vehicle (pre-specified definition of response)

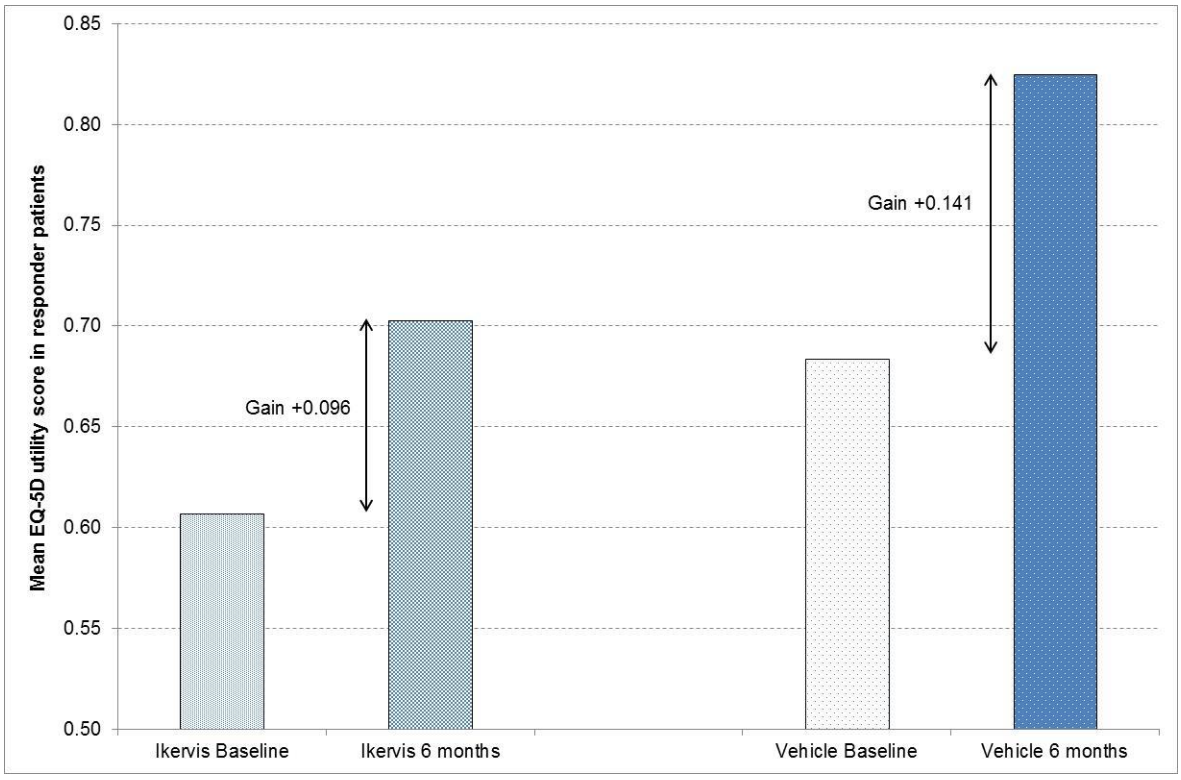


Figure 2 Comparison of utility gain associated with response to treatment for Ikervis and vehicle (post-hoc definition of response)

4.2 Revised cost effectiveness model results

Tables 4 and 5 present cost effectiveness results based on the revised decision model provided by the company in their response to the ACD requests. Starting with the new base case analysis, each of the issues in Table 3 are considered in turn and separate sensitivity analyses are shown when the alternative option (usually reversion to the company's original setting) is used instead. The ERG does not accept that the company's approach to calculating the costs of dispensed drugs in the revised model is appropriate. In response, the ERG has applied its preferred method in the form of two modifications that relate to drug costs during the clinical trial, and those projected beyond the trial period.

At the foot of each table, all of the options that the ERG considers to be appropriate are combined to give a preferred scenario, shown in aggregate as well as for patient subgroups.

It is clear from these analyses that for most of these model issues the option selected has only a minor effect on the size of the estimated ICER. Only the choice of the definition of response to treatment (pre-specified trial response vs post-hoc definition), and the choice of the basis for estimating the utility gain experienced by patients who respond to the treatment in the trial (separate treatment-specific values vs a single pooled average value for all patients) have a substantial impact on the relative cost effectiveness of Ikervis compared to the comparator.

Table 4 ERG sensitivity analyses relative to new company base case, assuming trial medication is used for 6 months

Model scenarios & revisions	Ikervis + AT		Vehicle + AT		Incremental		ICER	ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change
Revised Company base case scenario: All patients	£16,653	10.099	£15,492	10.074	£1,161	**0.025**	**£45,554**	-
SS sub-group only	£16,530	10.065	£15,689	10.046	£841	0.019	£44,874	- £680
Non-SS sub-group only	£16,727	10.120	£15,373	10.091	£1,354	0.030	£45,814	+£260
1. Revert to no AT use with plugs	£16,636	10.099	£15,475	10.074	£1,162	0.025	**£45,568**	**+£14**
2. Switch to Tx specific AT usage	£16,890	10.099	£15,829	10.074	£1,061	0.025	**£41,632**	**-£3,922**
3. Revert to excluding steroid costs	£16,428	10.099	£15,263	10.074	£1,165	0.025	**£45,690**	**+£136**
4. Switch to Tx-specific utilities (ERG)	£16,653	10.068	£15,492	10.102	£1,161	-0.035	**Dominated**	**N/A**
5. Use in-trial Tx costs (ERG)	£16,659	10.099	£15,592	10.074	£1,067	0.025	**£41,860**	**-£3,694**
6. Use monthly prescribing (ERG)	£16,743	10.099	£15,537	10.074	£1,206	0.025	**£47,313**	**+£1,759**
ERG preferred scenario *(applying revisions 4,5,6)*	£16,748	10.068	£15,637	10.102	£1,112	**-0.035**	**Dominated**	**N/A**

AT=artificial tears; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; N/A=not applicable; QALY=quality adjusted life year; SS=Sjögren's syndrome; Tx=treatment
Dominated=reduced incremental QALY benefit and increased incremental cost

Table 5 ERG sensitivity analyses relative to new company base case, assuming trial medication is used for 3 months

Model scenarios & revisions	Ikervis + AT		Vehicle + AT		Incremental		ICER	ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change
Revised Company base case scenario: All patients	£16,314	9.966	£15,687	9.940	**£627**	**0.025**	**£24,696**	-
SS sub-group only	£16,190	9.933	£15,842	9.920	£348	0.014	£25,350	+ £654
Non-SS sub-group only	£16,388	9.985	£15,594	9.953	£795	0.032	£24,529	-£167
1. Revert to no AT use with plugs	£16,296	9.966	£15,669	9.940	£627	0.025	**£24,711**	**+£15**
2. Switch to Tx specific AT usage	£16,576	9.966	£16,008	9.940	£568	0.025	**£22,401**	**-£2,295**
3. Revert to excluding steroid costs	£16,086	9.966	£15,456	9.940	£630	0.025	**£24,832**	**+£136**
4. Switch to Tx-specific utilities (ERG)	£16,314	9.944	£15,687	9.958	£627	-0.014	**Dominated**	**N/A**
5. Use in-trial Tx costs (ERG)	£16,319	9.966	£15,787	9.940	£532	0.025	**£20,985**	**-£3,711**
6. Use monthly prescribing (ERG)	£16,384	9.966	£15,747	9.940	£636	0.025	**£25,084**	**+£388**
ERG preferred scenario *(applying revisions 4,5,6)*	£16,390	9.944	£15,847	9.958	**£542**	**-0.014**	**Dominated**	**N/A**

AT=artificial tears; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; N/A=not applicable; QALY=quality adjusted life year; SS=Sjögren's syndrome; Tx=treatment
Dominated=reduced incremental QALY benefit and increased incremental cost

5 SUMMARY AND CRITIQUE OF COST-MINIMISATION ANALYSIS

In its original report, the ERG noted that different formulations of CsA are used in clinical practice in England. These include Restasis (0.05% CsA drops) imported from the USA and Optimmune (0.2% CsA ointment) which is an ophthalmic ointment and 2% eye drops. Although none of these CsA formulations are currently licensed for human use in the UK (Restasis is licensed for use in the USA whereas Optimmune is a veterinary product licensed used to treat dry eye in dogs), the ERG nevertheless considered that these were the most appropriate comparators for Ikervis. Acknowledging it was not possible to compare the clinical effectiveness of Ikervis with these other formulations, the ERG suggested that the only valid economic comparison available is a cost minimisation analysis i.e. to assume that all CsA based treatments are of equivalent efficacy, are associated with similar adverse events and incur similar administration, prescribing and monitoring costs. A simple cost-comparison of different CsA formulations was conducted by the ERG in its original report (and summarised in Table 3). Following the ERGs exploratory analysis and the committee's restated desire to see a scenario analysis comparing Ikervis to other CsA formulations in section 4.15 of the draft ACD, a similar analysis was also performed by the company (and also summarised in Table 3).

Table 3 Simple cost-comparison of different ciclosporin formulations*

Ciclosporin formulation	Monthly cost (ERG estimate)	Monthly cost (company estimate)
Ikervis	£72.00	£72.00
Restasis eye drops (0.05%) 0.4ml	£119.75	£454.20
Ciclosporin eye ointment, (0.2%)	£55.24	£227.10
Ciclosporin eye drops (2%)	£47.24	-
Hospital ciclosporin (weighted cost)	-	£367.59

* Adapted from page 64 of original ERG report and Table 31 of company's response to ACD

According to the company's analysis, the 2% CsA drops cited by the ERG are no longer available. Other important discrepancies between the ERG's and company's cost-comparisons are also noted. In particular, the company concluded that Ikervis is over £150 cheaper per month than Optimmune eye ointment, £382 cheaper than Restasis and almost £300 cheaper than their weighted average. The ERG, on the other hand, had previously concluded Ikervis was less costly than Restasis, but more costly than Optimmune.

The company states its costs are sourced from the NHS Drug Tariff but the ERG was unable to find any mention of either CsA product from this source; costs originally cited by the ERG

were derived from advice received from its clinical advisor (one of the authors of the original ERG report). The ERG notes that the company's costs are approximately four times higher than those it cited. A possible explanation for this may be that the company has assumed patients use one vial of Restasis or one tube of Optimmune every week, rather than one vial/tube per month as the ERG was advised to be the normal requirement.

6 OVERALL CONCLUSIONS

The company has responded to all of the requests made in the ACD, and this report summarises the ERG's assessment of this new evidence and analysis.

The company has presented a thorough and careful review of the clinical trial evidence available concerning the clinical effectiveness of various CsA formulations and found that the evidence base is too diverse and heterogeneous to allow a meaningful indirect treatment comparison to be carried out. The ERG concurs with this conclusion.

The company has responded to the request for a revised economic model that includes the various amendments requested by the Appraisal Committee. These are generally well implemented; however the ERG is not satisfied with the company's approach to treatment costs and has applied an alternative method.

In addition, the company has contested a key assumption underlying one of the changes requested (whether the utility gain from response to treatment should be a single pooled average, or be estimated separately for each treatment) and omitted this change from their revised base case analysis. The set of new cost effectiveness results presented here by the ERG demonstrates that this is the most important issue requiring a decision; if separate values are used then Ikervis is shown to be **not** cost effective under any scenario, but if a single pooled value is applied then a range of potentially cost effective scenarios may be available. The ERG reiterates its previously expressed view that the model is lacking any mechanism for evaluating adverse events (either in terms of costs or health-related utility) and the use of a single pooled average utility estimate automatically ensures that any differential in patient acceptability and tolerability of treatment included in the recorded EuroQol responses is thereby excluded from the model results.

This issue and the choice of which definition of response to treatment should be used in the analysis are the most important considerations in appraising the cost effectiveness of Ikervis in this population.

When conducting a simple cost-comparison of different CsA formulations, discrepancies exist between the company's and ERG's estimates. Both the company and ERG concur Ikervis is cheaper than Restasis but different conclusions have been reached in relation to the cost-comparison of Ikervis with Optimmune. This may be due to different assumptions about vial/tube use adopted by the company and ERG.

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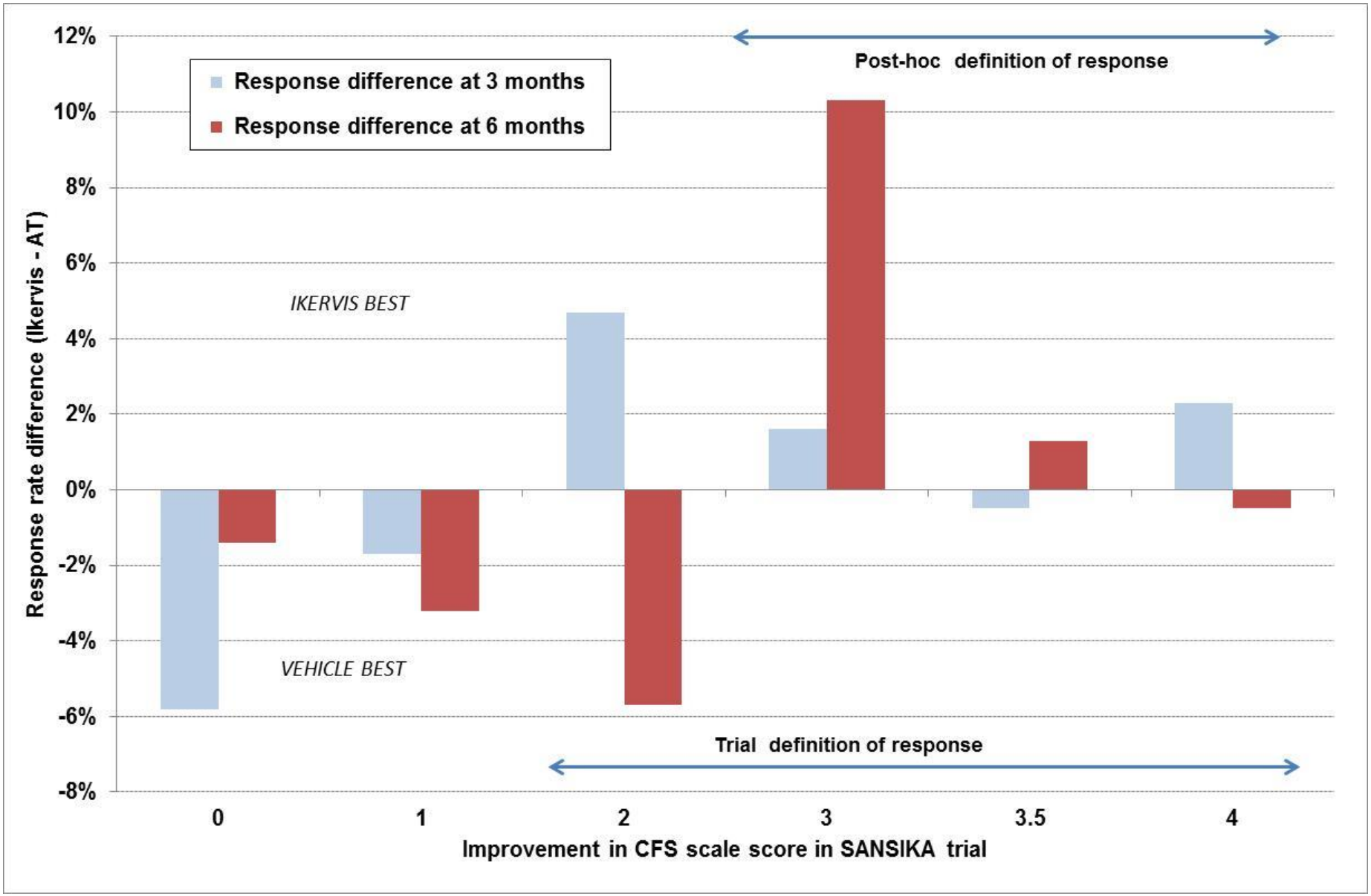
12%
10%
8%
6%
4%
2%
0%
-2%
-4%
-6%
-8%
Response rate difference (Ikervis - AT)
Response difference at 3 months
Response difference at 6 months
Post-hoc definition of response
IKERVIS BEST
VEHICLE BEST
Trial definition of response
0
1
2
3
3.5
4
Improvement in CFS scale score in SANSIKA trial

4.1 Utility change related to response to treatment

It is noteworthy that the only requested change which the company did not include in their revised base case analysis concerns the use of treatment-specific utility values for response to treatment.

The company presents results of a step-wise regression analysis to support their view that there is no justification for applying differential values to the utility gain according to the treatment received in the SANSIKA[4] trial. At first sight this appears to be a convincing argument in favour of their contention that utility results from the two trial arms should be pooled.

However, closer examination reveals that there is a systematic imbalance in the condition of responding patients (measured in terms of mean EQ-5D utility score) at the beginning of the SANSIKA[4] trial as shown in Figures 1 and 2. In addition it can be seen that the health-related quality of life benefit gained from a confirmed response to treatment is substantially greater in the vehicle arm of the SANSIKA[4] trial than in the intervention arm (1.7 times when the original trial definition of response is considered and 1.5 times with the post-hoc definition). It is also noticeable that the utility gain and the baseline utility value appear to increase in step. This raises the possibility that the inclusion of the baseline utility value, and perhaps other variables, into the company's regression analysis may have led to quite different results. In any case, it is clear that by pooling the two trial arms and assigning the same overall average utility gain to both treatments there is a risk of introducing a serious bias into the cost effectiveness analysis; this understates the utility gain recorded in the comparator arm of the trial and overstates the gain in the intervention arm.

The extent of this bias is evident in the results obtained from the new version of the company model (Tables 4 and 5), which show that the choice between separate and pooled utility gain estimates makes the difference between obtaining quantifiable incremental cost effectiveness ratios (ICERs), and Ikervis being dominated by the comparator (less effective and more costly). Clearly this is the most important issue influencing the estimation of cost effectiveness in this appraisal.

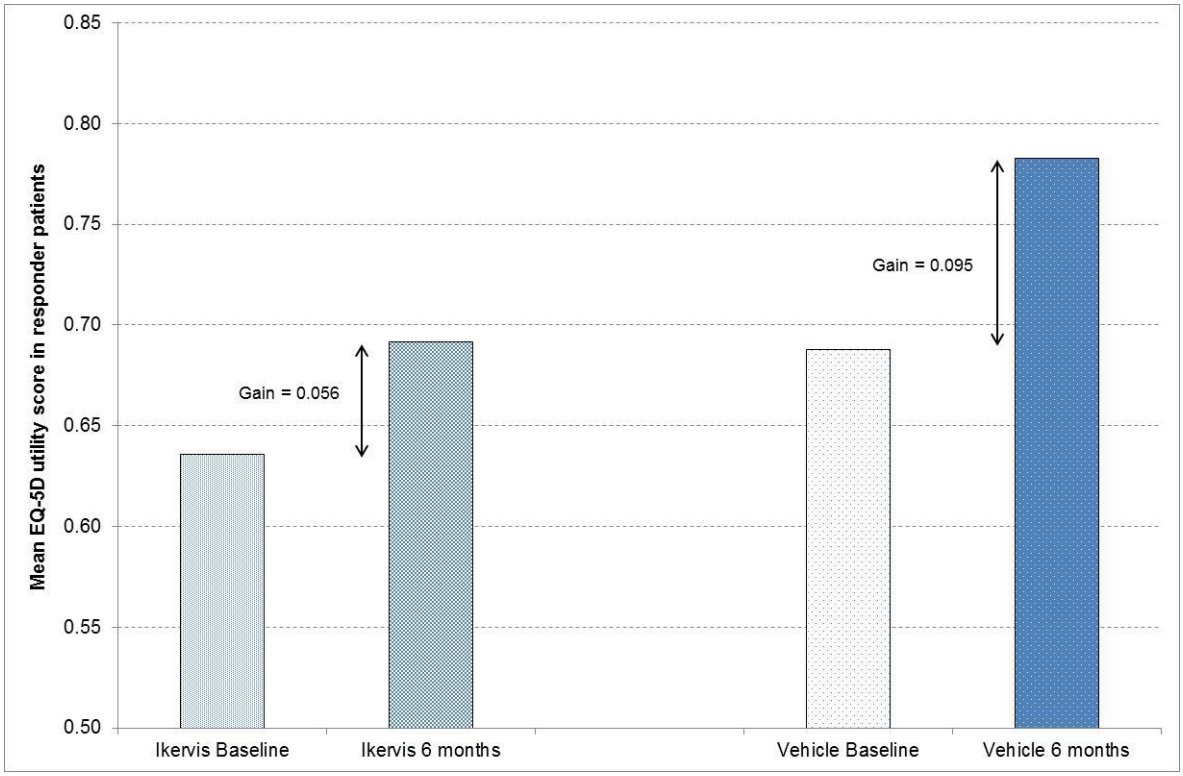

Figure 1 Comparison of utility gain in patients responding to treatment for Ikervis and vehicle (pre-specified definition of response)

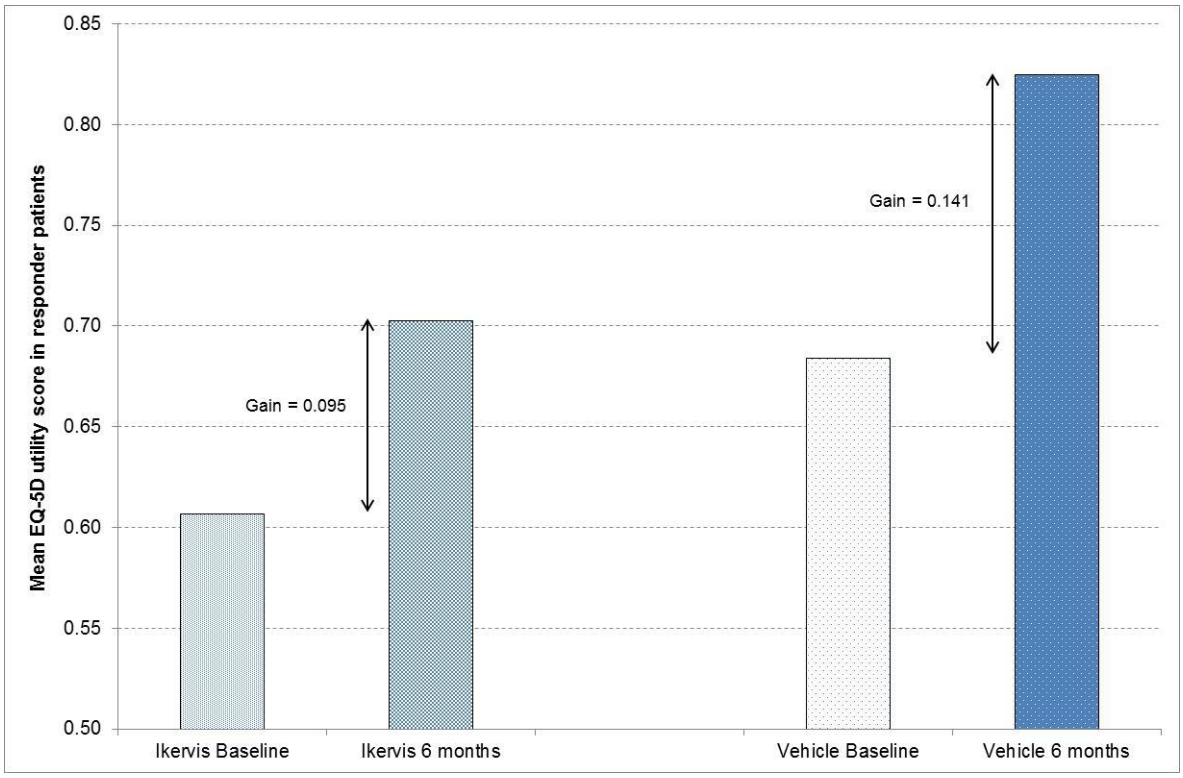

Figure 2 Comparison of utility gain in patients responding to treatment for Ikervis and vehicle (post-hoc definition of response)