NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ciclosporin for treating dry eye disease

This premeeting briefing presents:

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

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

Key issues for consideration

Clinical effectiveness

- Which comparator or comparators are the most appropriate for ciclosporin for treating dry eye disease that has not responded to tear substitutes?
  - The company presented clinical effectiveness evidence from SANSIKA and SICCANOVE which compared ciclosporin plus artificial tears with vehicle plus artificial tears. The company noted that vehicle may have beneficial effects on its own, whilst the ERG considered that the improvements may be as a result of vehicle, concomitant use of artificial tears or both vehicle and concomitant use of artificial tears.
  - The ERG considered that the appropriate comparator for ciclosporin is other individually-prepared pharmaceutical ciclosporin formulations currently used in clinical practice in the NHS without a marketing authorisation and ciclosporin formulations with a marketing authorisation outside the UK.

  - The NICE scope defines the comparator as standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments, and acute use of topical corticosteroids).
- How generalizable are the results from the randomised trials (SANSIKA and SICANOVE) to clinical practice in the NHS? Is SANSIKA more relevant to the decision problem than SICCANOVE?
  - SANSIKA included people with severe dry eye disease and SICCANOVE included people with moderate to severe dry eye disease. The company considered the results of SANSIKA to be more relevant to the decision problem and the ERG agreed with this.
  - The ERG further noted that only the results of post-hoc analyses for people with severe dry eye disease in SICCANOVE are relevant to the decision problem and that these should only be considered exploratory.
- What, if any, is the impact on the results of the different excipients used in the trials?
  - The company noted that the excipients included in the ciclosporin formulation in SANSIKA and SICCANOVE are different. It stated that ciclosporin formulations in SANSIKA and SICCANOVE are considered similar and that this was further confirmed by the CHMP during scientific advice.
  - The ERG noted that it is unclear whether the excipients should be considered similar and that the differences in the rate of some adverse effects found between these trials may be because of differences in the excipients and differences in severity of dry eye disease in the trial populations.
- Is the composite Corneal Fluorescein Score-Ocular Surface Disease Index (CFS-OSDI) end point clinically relevant and meaningful? If so, which criteria for response are more clinically appropriate? Has ciclosporin shown sufficient clinical effectiveness even though the primary end point in SANSIKA has not been met?
  - The primary end point in SANSIKA was response rate in a composite end point of signs (measured using CFS) and symptoms (measured using OSDI). The response definition was improvement of 2 points or more from baseline in CFS in the analysed eye, and improvement by 30% or more from baseline in OSDI. The results did not show statistically significant differences between ciclosporin

and vehicle in CFS-OSDI response rates and thus, results from SANSIKA did not meet its primary end point
  - When using a post-hoc, more strict, definition of response (where improvements in CFS were set at 3 points), there were statistically significant differences between ciclosporin and vehicle.
  - Ciclosporin also showed statistically significant improvements compared with vehicle in terms of CFS alone and HLA-DR, a measure of inflammation.
  - The ERG noted that the clinical relevance of the composite end point CFS-OSDI is unclear and that if it is considered clinically relevant, the threshold for the response definition remains uncertain.
  - The ERG also acknowledged that improvements in terms of CFS and HLA-DR shown with ciclosporin are encouraging and appear to show that ciclosporin has an anti-inflammatory effect, and that it may be speculated that any differences in signs would take longer to translate into differences in symptoms.
- Are the results of the meta-analysis valid and appropriate?

Cost effectiveness

- Is the company's model robust and valid to support decision making?
  - The company used the results from SANSIKA for its model and noted that it conservatively used the results from the vehicle plus artificial tears group as a proxy for the artificial tears group alone in the model.
  - The ERG considered that results from SANSIKA cannot be used directly to inform an economic evaluation because vehicle is not commercially available and thus, cannot be considered established clinical practice in the NHS.
  - The ERG suggested that the appropriate comparator for ciclosporin is other ciclosporin formulations.
- Is it appropriate to use the post-hoc definition of response of CFS-OSDI in the economic model?
  - The company used the post-hoc definition of CFS-OSDI response of SANSIKA, which is more restrictive than the pre-specified one, for its economic model.

  - The ERG noted that this has a big impact on outcomes estimates and the cost-effectiveness results and that the more restrictive definition excludes the level of benefit which most favours the vehicle group.
- Should a subgroup analysis for people with Sjogren syndrome have been presented in the cost-effectiveness section as stated in the NICE scope?
  - The company presented a subgroup analysis based on a meta-analysis of SANSIKA and SICCANOVE for the composite end point CFS-OSDI response rate only including people with Sjogren syndrome and severe dry eye disease. The results showed that the CFS-OSDI response rate at month 6 was statistically significantly higher with ciclosporin compared with vehicle.
  - The company did not conduct any cost-effectiveness analysis in this subgroup stating that because of the small number of patients it did not consider it feasible to conduct a cost-effectiveness analysis for this subgroup. The ERG agreed with the company's view and rationale.
- Does ciclosporin have an impact on monitoring and other health care resources?
  - The company assumed that administration, monitoring and testing costs with ciclosporin or artificial tears were zero because all treatments were self-administered and because it was assumed that the rate of ophthalmologist visits, tests and monitoring were similar in both treatment groups independently from the response status of the disease.
  - A professional group highlighted that patients having long-term systemic treatment with ciclosporin are at risk of infection and that the use of ciclosporin in clinical practice is accompanied by strict pre-treatment criteria and post-treatment monitoring.
- What is the most appropriate approach for incorporating utility values into the model?
  - The company applied pooled utility values from both treatment groups to the model in terms of response.
  - The ERG considered it would be more appropriate to apply different utility values by treatment group and response to treatment because people in the vehicle group in SANSIKA showed a larger utility benefit based on response compared with people in the ciclosporin group.

- What is the most appropriate approach to model stopping treatment?
  - The company applied probabilities for continuing treatment beyond the end of the trial from different time periods for each treatment group.
  - The ERG applied the Kaplan-Meier results for stopping treatment in SANSIKA.
- What is the most plausible ICER for ciclosporin plus artificial tears compared with vehicle plus artificial tears?
- Are the results of the ERG's cost-minimisation analysis relevant and valid for decision making?
  - The ERG conducted an exploratory cost-minimisation analysis comparing ciclosporin with other pharmaceutical ciclosporin formulations.

Innovation

- Is ciclosporin considered innovative for treating severe dry eye disease? Are there any other benefits from ciclosporin unlikely to be captured in the QALY calculation?
  - The company considered ciclosporin to be innovative and noted that other benefits are unlikely to be captured fully in the QALY calculation because:
    - it provides a clinically effective and safe option to people with severe dry eye disease with no available authorised active treatments
    - benefits in symptoms correlate poorly with objective clinical findings, the long term implications of a reduction in ocular surface inflammation and other objective improvements
    - it offers the benefit of administering 1 drop per day compared with, for example, a drop every 30 minutes needed with some artificial tears.

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ciclosporin within its licensed indication for treating dry eye disease.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with severe dry eye disease (DEWS 3 or 4) whose disease has not adequately responded to tear substitutes	Patients with dry eye disease and severe keratitis which has not improved despite treatment with tear substitutes.	The decision problem reflects the approved indication for ciclosporin. Patients with severe keratitis are a recognised subgroup of severe dry eye disease patients.	The criteria used to define severe dry eye disease in the NICE scope (DEWS) represent one set of criteria for measuring severe dry eye disease; the ERG is aware that criteria may vary between geographical areas and healthcare professionals in clinical practice. The population specified in the decision problem is identical to that of the proposed marketing indication for ciclosporin.
Int.	Ciclosporin	Ciclosporin	N/A	The ERG noted that the ciclosporin vehicle contains the CKC excipient whilst the ciclosporin formulation used in the supportive SICCANOVE trial contains BAK instead of CKC. The ERG,

				however, noted the different adverse effects profiles (rates of eye irritation, eye pain, site irritation and site pain and differences in rates of adverse effects severity) particularly in the intervention arm in the SANSIKA and SICCONOVE trials and suggested that this may be due to differences in the vehicle formulation and/or differences in severity of dry eye disease in the trial populations.
Com.	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)	The decision problem addressed in the submission does not vary substantially from the scope. However, in the absence of an approved and valid active comparator, the ciclosporin excipient (vehicle) was used as a comparator in the clinical trials, as recommended by the European Medicines Agency (EMA).	The ERG considered that other formulations of ciclosporin which are currently used in clinical practice in England are the most appropriate comparators. While Restasis (another formulation of ciclosporin which has a license in the US) is not licensed for use in Europe, the fact that it is currently used in clinical practice

			Artificial tears do not have any active properties and are usually the background treatment, or corticosteroids, which are well known for their local side effects (cataract, glaucoma) when used chronically, were all discussed and ruled out. In addition, comparison of ciclosporin to its vehicle was deemed necessary since eye drop vehicles are known to have some beneficial effect on their own.	in England means it can be considered as a relevant comparator. The ERG also considered that other formulations of ciclosporin (such as 2% ciclosporin eye drops and Optimmune ointment) should be considered comparators as they too are currently used in NHS practice.
Out.	• Eye pain and discomfort • Symptoms of dry eye disease (including photosensitivity, ability to open eyes, visual acuity and ability to concentrate) • Adverse effects of treatment • Health-related quality of life.	• Corneal staining (CFS) using modified Oxford scale • Oxford Surface Disease Index (OSDI) • CFS-OSDI responder (a patient satisfying the following conditions simultaneously: change from baseline in CFS $\leq$-2 and in OSDI $\leq$-30%) • Ocular discomfort (using a visual analogue scale (VAS)) • Inflammation (HLA-DR) • Tear film osmolarity	Regulatory guidance recommended studying both signs and symptoms of the disease. Objective outcomes such as inflammation, ocular surface disease, corneal staining and tear osmolarity were also evaluated to determine the impact of ciclosporin on eye health to provide additional clinically relevant information.	The ERG noted that the company emphasised the lack of correlation between signs and symptoms and agreed that measuring the impact of treatment on signs is as important as measuring impact on symptoms (as well as adverse effects and health-related quality of life). The ERG noted that the composite outcome used in SANSIKA has

		• Tear film break up time • Symptoms: burning, stinging, foreign body sensation, itching, eye dryness, pain, blurred vision or sticky feeling, photophobia (each assessed by a VAS) • Adverse effects of treatment • Health-related quality of life		not been validated and the clinical significance of changes in the outcome are unclear (although considered separately, the CFS and OSDI endpoints are meaningful).
Sub.	If the evidence allows, a subgroup analysis of people with Sjogren syndrome should be considered.	A subgroup analysis of patients with Sjogren syndrome has been presented in the clinical efficacy section.	In SANSIKA, approximately one third of the population had Sjogren syndrome, including 58 patients in the ciclosporin arm and 34 in the vehicle arm. It was not considered feasible to conduct a cost-effectiveness analysis on this small subset of patients.	The ERG agreed with the company's reasoning that the outcomes of this group of patients were considered in a subgroup analysis that was conducted for assessment of clinical effectiveness but not for cost effectiveness.

Abbreviations: Pop., population' Int., intervention; Com., comparators; Out., outcomes; Sub., subgroups; DEWS., dry eye disease workshop system; HLA-DR., human leukocyte antigen-DR; CKC., cetalkonium chloride; BAK., benzalkonium chloride

Source: adapted from company's submission, section 5, pages 34 – 37

2 The technology and the treatment pathway

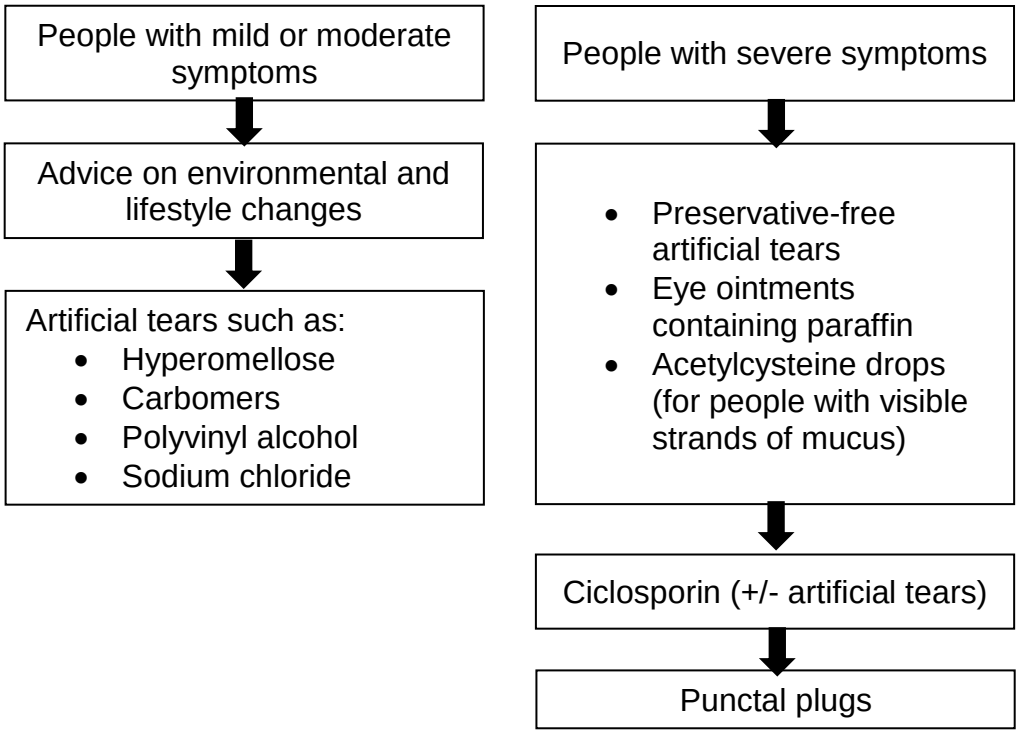
2.1 Ciclosporin (Ikervis, Santen) is a sterile, positively charged, oil-in water, unpreserved ophthalmic emulsion that contains ciclosporin (CsA) Ph Eur. Its formulation contains an excipient, cetalkonium chloride, that acts as a cationic agent and is specifically designed to prolong the time each eye drop stays on the epithelial layer of the eye. Ciclosporin has an anti-inflammatory effect on the cornea and the lacrimal (tear) gland reducing inflammation in the eye. Following administration, ciclosporin enters corneal and conjunctival infiltrated T-cells and subsequently blocks the expression of anti-inflammatory cytokines. It is administered as an eye drop (see Table 2).

2.2 Treatment for dry eye disease depends on the severity of the disease. The severity of the disease can be measured using the definition and classification of dry eye disease workshop system (DEWS), which describes 4 levels of disease severity, ranging from 1 (least severe) to 4 (most severe). People with a score of 3 to 4 are generally considered to have severe dry eye disease. The NICE Clinical Knowledge Summary for dry eye syndrome recommends providing advice on environmental and lifestyle issues to people with mild or moderate dry eye disease. If insufficient, artificial tears such as hyperomellose, carbomers, polyvinyl alcohol or sodium chloride should be considered. For people with severe symptoms, preservative-free artificial tears and ocular lubricant ointment containing paraffin (to use at night) are recommended. Acetylcysteine drops are considered to be appropriate for people with visible strands of mucus. Some people may also need surgery with punctal plugs (see Figure 1 Treatment pathway). The company noted that moderate to severe dry eye disease is usually managed by ophthalmologists who provide regular updates to the GP. The company also stated that individually-prepared ciclosporin pharmaceutical formulations are currently used in the NHS although these formulations do not have marketing authorisations in Europe for this indication, are poorly controlled in terms

of manufacturing quality and formulation, and their efficacy has not been clearly demonstrated. The company also noted that the excipients (referred to as vehicle hereafter) used by different companies that manufacture other ciclosporin formulations, are considered to be different in terms of their efficacy and tolerability.

2.3 The company stated in its submission that because there is no standard or authorised active treatment for severe dry eye disease which has not improved despite treatment with tear substitutes, the ciclosporin vehicle was used as a comparator in the clinical trials, as recommended by the European Medicines Agency (EMA). It noted that eye drop vehicles are known to have some beneficial effect on their own. For its economic model the company chose to align to routine UK clinical practice and assumed that vehicle is not routinely available and so the comparator was standard care with and without ciclosporin.

Figure 1 Treatment pathway



Source: adapted from Clinical Knowledge Summary: Dry eye syndrome, September 2012 and company's submission, section 2.4 page 24

Table 2 Intervention and comparators

	Ciclosporin	Artificial tears
Marketing authorisation	On 22 January 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for ciclosporin. The approved indication is: "Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes".	Polyvinyl alcohol: Symptomatic relief of dry eye and symptomatic relief of eye irritation associated with deficient tear production. Carbomer: Substitute tears fluid for the management of dry eye conditions including keratoconjunctivitis sicca, and for unstable tear film. Eye Ointment Liquid paraffin 10%, wool fat 10%, in yellow soft paraffin, 4g: To lubricate and protect the eye in conditions such as exposure keratitis, decreased corneal sensitivity, recurrent corneal erosions, keratitis sicca, ophthalmic and non-ophthalmic surgery, sticky eyes and to soften crusts formed due to inflammation of the eye lids.
Pharmaceutical formulation	Active ingredient: ciclosporin Ph. Eur. (CsA) (0.1% w/w/) Excipient: Cetalkonium chloride (CKC)	Single use Liquifilm Tears: polyvinyl alcohol 1.4%, povidone 0.6% Single use Viscotears: carbomer 980 (polyacrylic acid) 0.2% Liquid paraffin 10%, wool fat 10%, in yellow soft paraffin, 4g
Administration method	Topical (eye drop) One drop of 1 mg/ml Once daily at bedtime	Topical (eye drops) Starting number of drops per eye per day: 14.89 Each single use vial of polyvinyl alcohol and carbomers is assumed to be able to treat both affected eyes.
Average length of treatment	The company stated that historically, the average duration of treatment for dry eye disease ranges from 20 weeks (in Italy) to 52 weeks (Germany and Spain) and that it did not anticipate that this would be substantially different for ciclosporin.	Lifelong (except for people who have surgery with permanent punctal plugs).
Acquisition cost (excluding VAT)	£72	Polyvinyl alcohol: £5.35 Carbomers: £5.42 Paraffin: £3.25
Average cost of a course of treatment	The company noted that the average cost of a course of treatment is unknown. In its economic modelling the company assumed that	Cost of treatment with artificial tears per month: £44.40

	patients whose disease has not responded by month 6 stop treatment. Cost of treatment with ciclosporin plus artificial tears per month: £110.67	
See summary of product characteristics for details on adverse reactions and contraindications. Source: company's submission, pages 19, 181, 182 and 183		

3 Comments from consultees

3.1 A professional group noted that treatment for dry eye disease is guided by the severity of the condition based on the DEWS classification system and ranges from topical lubricants for DEWS 1 to immunosuppressants and surgery for DEWS 3 – 4. It stated that different individually-prepared pharmaceutical ciclosporin formulations are currently used without a marketing authorisation in clinical practice for people with dry eye disease and DEWS 3 – 4. The professional group also noted that artificial tears are sometimes used as an add-on treatment with ciclosporin.

3.2 The professional group noted that ocular symptom relief is really important to patients and that other outcome measures such as amelioration of tear film break up time, reduction in the frequency of lubricant use and the Schirmer tear function test have been used in clinical trials and are replicable in clinical practice.

3.3 The professional group highlighted that patients having long-term systemic treatment with ciclosporin are at risk of infection and that the use of ciclosporin in clinical practice is accompanied by strict pre-treatment criteria and post-treatment monitoring. These include:

- specifications about contraindications to ciclosporin particularly in people with uncontrolled arterial hypertension, uncontrolled infections (including viral) and malignancies, impaired renal function and pregnant and older people
- complete medical history

- complete drug history including self-administered medications and dietary supplements
- tests to measure blood pressure, blood sugar levels and weight
- other laboratory tests
- advice and information for patients.

3.4 The professional group noted that because different ciclosporin formulations are being used in the UK without a marketing authorisation, it needs increased care and supervision in secondary care. The professional group stated that if ciclosporin were to be prescribed in the secondary care setting, it would be necessary to put measures in place to monitor the effectiveness and side effects of the treatment and progression of the condition. It highlighted that the prescription of ciclosporin eye drops should be part of a shared decision-making approach between clinicians and patients. It also noted that NHS staff would need additional training for the prescription, supply and administration of ciclosporin.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic review and identified 2 main multicentre (including the UK) double-masked, randomised controlled clinical trials relevant to the decision problem, SANSIKA and SICCANOVE. These trials compared ciclosporin with a vehicle in people with dry eye disease which has not improved despite treatment with tear substitutes. The company also identified other trials studying the US formulation of ciclosporin (not licensed in the UK) but these were not considered to be relevant to the decision problem and not included in its submission.

4.2 SANSIKA (n=246) included people with severe keratitis and severe dry eye disease defined as having a Corneal Fluorescein Score (CFS) of 4 on the modified Oxford scale, a Schirmer score (without anaesthesia) of 2

mm or more and less than 10 mm and an Ocular Surface Disease Index (OSDI) score of 23 or more. It compared ciclosporin with a vehicle and patients were allowed to use preservative-free artificial tears as needed. The vehicle used for the ciclosporin formulation in SANSIKA was cetalkonium chloride. The company explained that cetalkonium chloride replaced benzalkonium chloride (which was used in SICCANOVE) because cetalkonium chloride is the most lipophilic of the 3 homologues in benzalkonium chloride. SANSIKA was designed in 2 parts; part 1 studied the efficacy of ciclosporin during 6 months and part 2 (24 week open-label extension) assessed the long-term safety of ciclosporin up to 12 months (n=207). Randomisation was stratified by centre. The investigator could be unmasked if a serious adverse event occurred and masking information would influence the patient's management. Once unmasked, the patient was excluded from the study from this point onwards. Treatment compliance was measured by the number of used and unused containers of ciclosporin in relation to the duration of the follow-up interval. The company noted that SANSIKA is the trial that best represents the population defined in the scope.

4.3 People in SICCANOVE (n=492) had moderate to severe dry eye disease defined as CFS from 2 to 4 on the modified Oxford scale, a Schirmer score (without anaesthesia) of 2 mm or more and less than 10 mm, a score of 4 or more on Lissamine green staining and a Tear Break-Up Time (TBUT) score of 8 seconds or less. Randomisation was stratified by Sjogren syndrome. Treatment compliance was measured by asking the patient or legal representative(s) about compliance with the dose regimen of ciclosporin (once daily at bedtime in both eyes). The vehicle used for the ciclosporin formulation in SICCANOVE was benzalkonium chloride. The company noted that benzalkonium chloride was used because of its extensive use in approved ophthalmic formulations and so, this formulation was used in the initial pharmaceutical, non-clinical and clinical development. The company stated that ciclosporin formulations in

SANSIKA and SICCANOVE are considered similar and that this was further confirmed by the CHMP during scientific advice.

4.4 Both trials included study visits at months 0, 1, 3 and 6 and in part 2 of SANSIKA, study visits took place at months 9 and 12. The company noted that patient baseline characteristics were well balanced between treatment groups in both trials in terms of age, gender, Sjogren syndrome, CFS score, OSDI score and Schrimer test score (see company's submission table B5 page 64 for complete details of patient baseline characteristics in SICANNOVE and SANSIKA).

4.5 The primary end points in SICCANOVE were change from baseline in CFS at month 6 measured using the modified Oxford grading scale and change from baseline in ocular discomfort at month 6 assessed using a global score, which was the mean of 8 individual symptoms (burning/stinging; itching; foreign body sensation; blurred vision; eye dryness; photophobia; pain and sticky feeling) measured with the visual analogue scale (VAS). A negative change from baseline indicated an improvement. In SANSIKA, the primary end point was change from baseline in CFS-OSDI at month 6, a composite variable combining the CFS and OSDI scores. The definition of response using CFS-OSDI was:

- improvement of 2 points or more from baseline in CFS in the analysed eye, and
- improvement by 30% or more from baseline in OSDI.

Secondary end points included change from baseline in CFS, ocular discomfort and CFS-OSDI analysed at other time points, use of concomitant artificial tears, investigator global evaluation of efficacy, Schirmer test (without anaesthesia) in both eyes, human leukocyte antigen-DR (HLA-DR) expression on the conjunctival cell surface by impression cytology, TBUT in both eyes, corneal and conjunctival staining assessed using the Van Bijsterveld grading system (Lissamine Green Staining), tear film osmolarity in both eyes and quality of life measured

with the EuroQol 5D Questionnaire (EQ-5D) and the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). Adverse events were analysed separately for ocular and systemic adverse events.

4.6 In both trials, the efficacy end points were analysed based on the full analysis set (n=489 in SICCANOVE, n=245 in SANSIKA part 1 and n=207 in SANSIKA part 2) which included all patients who received any amount of study drug and for whom post-baseline data were available. Statistical significance was set at a significance level of 5% ($p \leq 0.05$). The company used the last observation carried forward method for imputing missing values. The company also conducted different analyses for imputing missing data to check the influence of the method on the efficacy estimate. The analyses for the safety end points were based on the safety analysis set (n=492 in SICCANOVE, n=244 in SANSIKA part 1 and n=207 in SANSIKA part 2) which included all patients for whom there was any evidence that they used the study medication. For the analysis of efficacy end points in SICCANOVE, the country effect and treatment by country interaction were investigated and unless the treatment by country interaction was statistically significant at a significance level of 10%, data from all centres and countries were pooled in the reported analyses. In SANSIKA efficacy analyses centres were pooled by country and further pooling of countries was carried out based on geographical and cultural considerations as follows:

- Belgium, UK and France
- Czech Republic, Austria and Germany

For the efficacy analyses, the interaction between treatment and Sjogren condition was also investigated and considered to be statistically significant at a significance level of 20%.

4.7 The company conducted post-hoc subgroup analyses in people with more severe dry eye disease in SICCANOVE (CFS of 4) and in people with CFS of 3 or more and OSDI score of 23 or more at baseline. For

SANSIKA the company carried out several post-hoc subgroup analyses including analysis of the primary efficacy end point CFS-ODSI response rate setting the threshold of improvement of CFS at 3 grades instead of 2. For full details of the company's post-hoc analysis, see section 6.3.7, page 90 of the company's submission.

ERG comments

4.8 The ERG considered SICCANOVE and SANSIKA to be at low risk of bias and noted that in both trials efficacy was measured in terms of signs and symptoms, and adverse effects, all of which are important outcomes to clinicians and patients. The ERG also noted that SANSIKA included health-related quality of life data. It stated that the trials appear to be generalizable to clinical practice in England in terms of patient characteristics. The ERG did not consider that any of the differences in patients' baseline characteristics between groups would benefit any treatment over the other.

4.9 The ERG noted that only 17% of patients included in SICCANOVE had severe dry eye disease (as per the definition used in SANSIKA) and that the company presented post-hoc analyses for these. The ERG considered that these post-hoc analyses were appropriately used to inform pre-specified analyses in SANSIKA and agreed with the company that evidence from SANSIKA is more relevant to the decision problem.

4.10 The ERG considered that the value of the evidence from SANSIKA is limited because the comparator is the ciclosporin vehicle, rather than any of the comparators specified in the NICE scope. The ERG noted that the vehicle is not commercially available; it is not currently used in routine clinical practice. The ERG considered that the improvements may be because of vehicle itself, concomitant use of artificial tears or both vehicle and concomitant use of artificial tears. The ERG considered that the relevant comparator for ciclosporin was other ciclosporin formulations currently used in clinical practice in England. However, the ERG noted that because there are no trials comparing ciclosporin with other

pharmaceutical ciclosporin formulations, the absence of a common comparator and the differences in vehicles used in each formulation, it was not possible to conduct a robust indirect comparison.

4.11 The ERG highlighted that whereas there was no restriction in concomitant artificial tears use in SANSIKA, artificial tears use was allowed for a maximum of 6 drops per day in SICCANOVE. The ERG also noted that it is unclear whether the vehicle used in SANSIKA (cetalkonium chloride) should be considered similar to that used in SICCANOVE (benzalkonium chloride). The ERG noted that the rate of some adverse effects (eye irritation, eye pain, site irritation and site pain) was different between these trials and considered that this may be because of differences in the excipients.

4.12 The ERG commented on the clinical relevance of the composite primary end point in SANSIKA (CFS-OSDI response defined as improvement of 2 points or more from baseline in CFS in the analysed eye, and improvement by 30% or more from baseline in OSDI). It noted that both CFS and OSDI are recognised and validated outcomes to measure signs and symptoms respectively but was concerned that the validity of the composite end point is unknown. The ERG stated that it is unclear whether CFS-OSDI response is a clinically relevant end point and what the response thresholds should be to define a response. It also noted that the response thresholds would also depend on the criteria used for defining severe dry eye disease.

Clinical trial results

4.13 The company presented the results from SICCANOVE and SANSIKA for the primary end points. Results from SICCANOVE showed that there was a statistically significant reduction in CFS from baseline to month 6 with ciclosporin compared with vehicle (p=0.009). None of the results presented for the primary end point in SANSIKA were statistically significant (see Table 3). The company stated that there are many possible explanations for the disassociation in the differential results

between ciclosporin and vehicle including the lack of correlation between signs and symptoms in dry eye disease and the possible beneficial effects of the vehicle itself.

Table 3 Clinical trial outcomes in SICCANOVE and SANSIKA

SICCANOVE (NVG06C103)				**SANSIKA (NVG10E117)**			
	Ciclosporin	Vehicle	p-value		Ciclosporin	Vehicle	p-value
Co-primary endpoint: CFS score: change from baseline at Month 6 – FAS				**Composite primary endpoint: CFS-OSDI response at Month 6 – FAS Imputed data (according to the randomised treatment group)**			
n	241	248	p=0.009	N	154	91	p=0.326
Mean±SD	-1.05± 0.98	-0.82 ± 0.94		Responders, n (%)	44 (28.6)	21 (23.1)	
Median	-1.0	-1.0		Non-responders, n (%)	110 (71.4)	70 (76.9)	
Range (min, max)	(-4.0; 2.0)	(-3.0; 1.0)					
Global Score of Ocular Discomfort (VAS)				**Composite primary endpoint: CFS-OSDI response at Month 3 – FAS Observed data (according to the randomised treatment group)**			
n	238	245	p= 0.808	N	138	89	NR
Mean±SD	-12.82 ± 18.59	-11.21 ± 19.35		Responders, n (%)	31 (22.6)	12 (13.5)	
Median	-12.50	-8.54		Non-responders, n (%)	107 (77.6)	77 (86.5)	
Range (min, max)	(-62.1; 42.3)	(-74.8; 43.0)		**Composite primary endpoint: CFS-OSDI response at Month 6– FAS Observed data (according to the randomised treatment group)**			
				N	131	82	p=0.152
				Responders, n (%)	43 (32.8)	20 (24.4)	
				Non-responders, n (%)	88 (67.2)	62 (75.6)	
				CFS response at Month 6 – FAS (change in CFS of 2 or greater)			
				N	154	91	p= 0.346
				Responders, n (%)	80 (51.9)	41 (45.1)	
				Non-responders, n (%)	74 (48.1)	50 (54.9)	

	OSDI response at Month 6- FAS (change in OSDI of 30% or greater)			
	N	154	91	p=0.939
	Responders, n (%)	61 (39.6)	36 (39.6)	
	Non-responders, n (%)	93 (60.4)	55 (60.4)	

Abbreviations: CFS, Corneal staining; OSDI, Oxford Surface Disease Index; VAS, Visual Analogue Scale; FAS, full analysis set
Source: adapted from company's submission, table B10, pages 97 and 98

4.14 The company presented several analyses for secondary end points and post-hoc analyses from SANSIKA. For an overview of the statistical significance of these end points see Table 4. For further details on the results of the end points which showed statistically significant differences between treatment groups see sections 4.15 – 4.18 below.

Table 4 Statistical significance of end points at 6 months in SANSIKA

End points at 6 months	SANSIKA: statistically significance between treatment groups
Signs & Symptoms (composite outcomes)	
% responders of CFS (≥2) and OSDI (≥30%)	✗ Primary
% responders of CFS (≥3) and OSDI (≥30%) (observed data)	✓post-hoc
Signs	
Change in CFS	✓
CFS improvement of ≥2 points	✗
CFS improvement of ≥3 points (observed data)	✓post-hoc
Complete corneal screening	✗
% complete responders based on CFS	✗
Change in Schirmer's Test score without anaesthesia	✗
Change in lissamine green staining score	✗
Change in TBUT	✗
Impression cytology: HLA-DR (AUF)	✓
Impression cytology: HLA-DR expression (HLA-DR+)	✗
Mean (SD) tear film osmolarity	✗
Worst tear film osmolarity	✓ post-hoc ¥
Symptoms	
Change in global ocular discomfort (VAS)	✗
% of responders based on improvement in ocular symptoms (VAS) §	✗
Change in OSDI	✗
OSDI response: improvement of ≥ 30%	✗
Other	
Median use of artificial tears	✗
Investigator global evaluation of efficacy	✗

Abbreviations: CFS= corneal fluorescein staining; HLA-DR= human leukocyte antigens DR; N/A=not applicable (analysis of this outcome not conducted); OSDI= Ocular Surface Disease Index; SD=standard deviation; TBUT= tear film break up time; VAS=visual analogue scale
✓statistically significant; ✗ not statistically significant
¥ SANSIKA post-hoc subgroup analysis in patients with elevated tear film osmolarity at baseline
§ ≥30% global ocular discomfort (SANSIKA)
Source: adapted from ERG report, table 8, page 40

4.15 The company presented an analysis of CFS score change from baseline over time in SANSIKA. The results showed a statistically significant decrease in CFS score over time in both treatment groups ($p<0.001$). It noted that there was a statistically significant benefit with ciclosporin compared with vehicle over the 6-month treatment period ($p=0.017$). At 6 months, the decrease in CFS score from baseline was statistically significantly greater with ciclosporin than with vehicle ($p=0.037$) (for further details see company's submission, figure B5, page 106).

4.16 The company also analysed CFS-OSDI response rate over time in SANSIKA using a generalised mixed model. The results showed that when considering all study visits, CSF-OSDI response rate was statistically significantly higher with ciclosporin compared with vehicle ($p=0.043$) (for complete results see company's submission, table B17, page 113).

4.17 The company also conducted a post-hoc analysis of the composite end point CSF-OSDI but using an improvement of 3 grades or more in CSF as criteria for improvement in SANSIKA (see Table 5). It noted that based on imputed and observed data there was a statistically significantly higher response with ciclosporin compared with vehicle ($p=0.016$ and $p=0.012$ based on imputed and observed data respectively).

Table 5 CFS (at least 3 Grades Improvement)-OSDI response at month 6 (FAS) in SANSIKA

	Ciclosporin	Vehicle	p-value^
Imputed data (according to the randomized treatment group)			
N	154	91	p=0.016
Responders, n (%)*	29 (18.8)	7 (7.7)	
Non-responders, n (%)	125 (81.2)	84 (92.3)	
Observed data			
N[ł]	131	82	p=0.012
Responders, n (%)*	28 (21.4)	7 (8.5)	
Non-responders, n (%)	103 (78.6)	75 (91.5)	

Abbreviations: CFS, Corneal staining; OSDI, Oxford Surface Disease Index; FAS, Full analysis set
*CFS (at least 3 grades improvement)-OSDI responder: improvement of 3 points or more from Baseline in CFS in the analysis eye (i.e. change in CFS □-2) and improvement by 30% or more from Baseline in OSDI (i.e. % change ≤-30%).
^p-value for treatment effect in the logistic regression model.
[ł]Total sample size for this analysis was 213 (131+82 patients), i.e. there were 32 missing data.
Source: adapted from company's submission, table B16, page 111

4.18 Results of HLA-DR in SANSIKA showed that at 6 months ciclosporin was associated with a statistically significant decrease in HLA-DR from baseline compared with vehicle (p=0.021) showing that ciclosporin provided an anti-inflammatory effect. The company noted that this is important because dry eye disease is an inflammatory ocular disease evidenced by the inflammatory changes that occur on the entire ocular surface.

4.19 The company noted that it presented the median use of artificial tears instead of the mean use because the distribution of the data was skewed. It stated that there were no differences in the use of artificial tears between treatment groups during all visits in part 1 in SANSIKA but noted

that the number of missing data was high. The company stated that considering all available data, there was a progressive decrease in the use of artificial tears over time in both treatment groups. The results in part 2 showed a steady decrease in the use of artificial tears during the first 6 months in both treatment groups (-3.8 and -2.6 drops per day per eye in people who had ciclosporin in both parts of SANSIKA and in people who had vehicle in part 1 and ciclosporin in part 2 respectively). The company noted that the changes observed during the last 6 months were small (+0.3 and -0.6 drops per eye per day in people who had ciclosporin in both parts of SANSIKA and in people who had vehicle in part 1 and ciclosporin in part 2 respectively).

4.20 The company also analysed CFS-OSDI response rate in part 2 of SANSIKA. It noted that responses were similar in both treatment groups at months 9 and 12. For people who had ciclosporin in both parts of SANSIKA, the response rate increased up to 39.1% at month 12. This response rate increased up to 38% at month 12 in people who had vehicle in part 1 and switched to ciclosporin in part 2 of SANSIKA.

4.21 The company presented the health-related quality of life results from SANSIKA using the NEI-VFQ-25 and EQ-5D questionnaires. The results using NEI-VFQ-25 were similar between treatment groups at baseline and at 6 months but there was an increase in the mean NEI-VFQ-25 composite score over time in both treatment groups. There were no differences in the EQ-5D summary index and the EQ-5D VAS score between baseline and month 6 in both treatment groups and there were no differences between treatment groups either (see Table 6). The company noted that the tariff used to estimate the health utility values was based on UK data from 1993 (Rabin et al, 2011).

Table 6 EQ-5D summary index over time and change from baseline in part 1 of SANSIKA

	Ciclosporin N=154	Vehicle N=91	CMH test^	
			Effect	p-value
EQ-5D – Summary index				
Baseline	N=149	N=87		
Mean±SD	0.66±0.30	0.66±0.26		
Median	0.73	0.73		
Range (min;max)	(-0.4;1.0)	(-0.2;1.0)		
Month 6	N=124	N=78		
Mean±SD	0.68±0.32	0.69±0.27		
Median	0.76	0.74		
Range (min;max)	(-0.5;1.0)	(0.0;1.0)		
Change from Baseline at Month 6	N=121	N=75		
Mean±SD	0.02±0.25	0.02±0.21		
Median	0.00	0.00	Treatment	p=0.808a^
Range (min;max)	(-0.9;0.8)	(-0.8;0.7)		

Abbreviations: EQ-5D, EuroQol 5D; min., minimum; max., maximum; SD, standard deviation

^The p-value of the non-parametric Cochran-Mantel-Haenszel (CMH) test was considered instead of the analysis of covariance (ANCOVA) p-value because the distribution of the residuals was not normal (as evaluated by the Shapiro-Wilk test). For the same reason, adjusted means for baseline values (ANCOVA) were not provided.

Source: adapted from company's submission, table B20, page 130

ERG comments

4.22 The ERG noted that there was no statistically significant difference between treatment groups in the primary end point (CFS-OSDI response)

in SANSIKA. It also noted that the difference in CFS-OSDI response rate was greater in the severe dry eye disease population in SICCANOVE (25.2%) compared to SANSIKA (5.4%) and that this is because there was a lower response rate in the vehicle group in SICCANOVE (5.6%) than in SANSIKA (23.1%). The ERG explained that the reasons for that difference is unclear but that it may be because of different artificial tears use in the trials as mean use of artificial tears was higher in both treatment groups in SANSIKA compared with SICCANOVE. The ERG also noted that only 2 pre-specified measures of signs of dry eye disease (CFS and HLA-DR) showed statistically significant differences between treatment groups in SANSIKA and that there were no statistically significant differences in any measure for symptoms between ciclosporin and vehicle. The ERG considered that based on the statistical analyses the clinical superiority of ciclosporin compared with vehicle has not been demonstrated.

4.23 The ERG noted that improvements were reported over time for all efficacy outcomes in both treatment groups in SANSIKA and considered that this suggests that vehicle may have some therapeutic benefit. It however noted that it is unclear whether the improvements occurred as a result of the vehicle, as a result of concomitant artificial tears use or as a combination of both.

4.24 The ERG reviewed a systematic review provided by the company during the clarification process comparing different formulations of ciclosporin. The ERG considered the comparisons to be crude and emphasised that the results should not be considered as robust but noted that it suggests that ciclosporin (Ikervis) compares favourably with Restasis in terms of CFS and OSDI but with a possible increase in adverse effects.

Meta-analyses

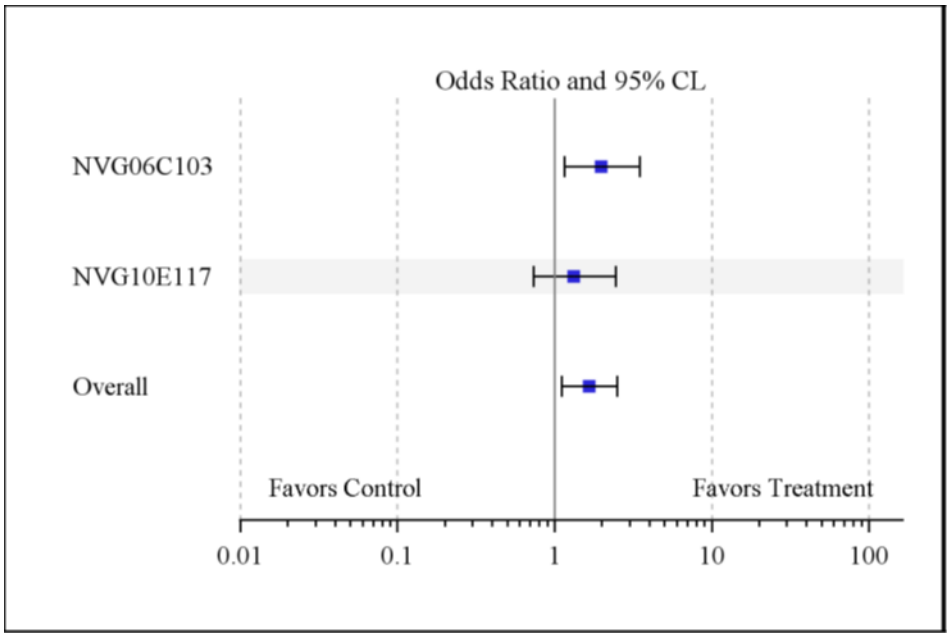
4.25 The company presented the results of a meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI response rate at 6 months for all patients. The results showed that the response rate was

statistically significantly higher with ciclosporin (21.6%) compared with vehicle (13.1%) at 6 months (p=0.015*) (see Table 7 and Figure 2).

Table 7 Meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in all FAS patients

		Ciclosporin (n=393*)		**Vehicle (n=336*)**	
SANSIKA		**n**	**%**	**n**	**%**
	Responders	44	28.6	21	23.1
	Non-responders	110	71.4	70	76.9
	Total	154	100	91	100
SICCANOVE		**n**	**%**	**n**	**%**
	Responders	41	17.2	23	9.4
	Non-responders	198	82.8	222	90.6
	Total	239	100	245	100
SANSIKA + SICCANOVE		**n**	**%**	**n**	**%**
	Responders	85	21.6	44	13.1
	Non-responders	308	78.4	292	86.9
	Total	393	100	336	100
Logistic regression with Treatment Study Interaction p-value (Treatment)= 0.015* p-value (Study)= <0.001 p-value (Pooled country)= 0.533 p-value (Treatment Study interaction)= 0.333 Abbreviations: CFS, Corneal staining; OSDI, Oxford Surface Disease Index; FAS, full analysis set Source: adapted from company's response to clarification, table A9 v.1 *p value taken from the draft EPAR and confirmed by the company to be correct N confirmed by the company to be correct					

Figure 2 Forest plot for the meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in all FAS patients



Notes: NVG06C103, SICCANOVE; NVG10E117, SANSIKA; FAS, Full analysis set

Source: company's response to clarification, figure A9 v.2

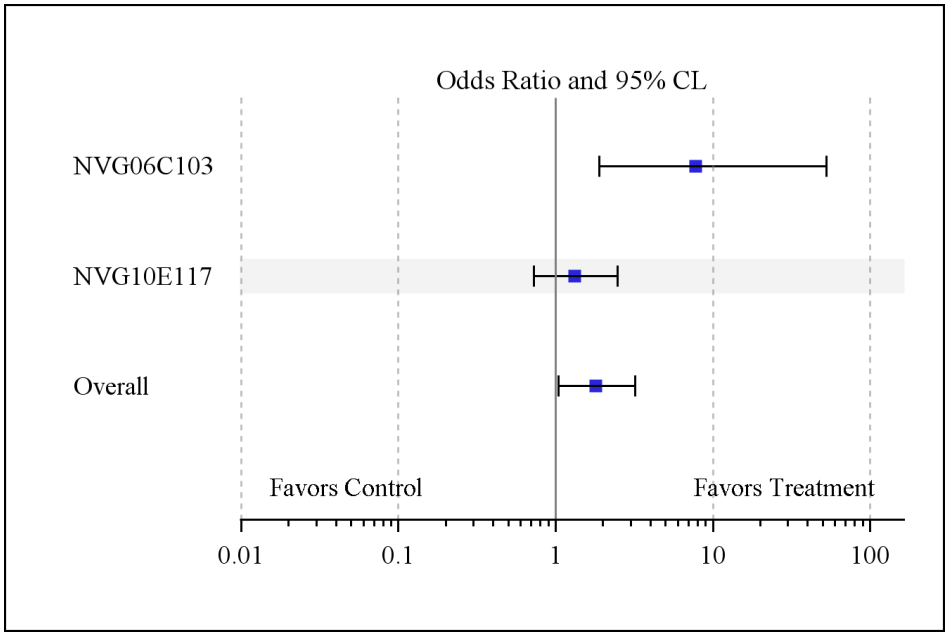
4.26 The company also presented a meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI response rate at 6 months in patients with severe dry eye disease (CFS score of 4 and OSDI score of 23 or more). The results also showed that the response rate was statistically significantly higher with ciclosporin (29.5%) compared with vehicle (18.3%) at 6 months (p=0.038*) (see Table 8 and Figure 3).

Table 8 Meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in FAS patients with severe dry eye disease

		Ciclosporin (n=193)		**Vehicle (n=126)**	
SANSIKA		**n**	**%**	**n**	**%**
	Responders	44	28.6	21	23.1
	Non-responders	110	71.4	70	76.9
	Total	154	100	91	100
SICCANOVE		**n**	**%**	**n**	**%**
	Responders	13	33.3	2	5.7

	Non-responders	26	66.7	33	94.3
	Total	39	100	35	100
SANSIKA + SICCANOVE		**n**	**%**	**n**	**%**
	Responders	57	29.5	23	18.3
	Non-responders	136	70.5	103	81.7
	Total	193	100	126	100
Logistic regression with Treatment Study Interaction p-value (Treatment)= 0.038* p-value (Study)= 0.150 p-value (Pooled country)= 0.188 p-value (Treatment Study interaction)= 0.041 Abbreviations: CFS, Corneal staining; OSDI, Oxford Surface Disease Index; FAS, full analysis set Source: adapted from company's response to clarification, table A9 v.2 *p value taken from the draft EPAR and confirmed by the company to be correct					

Figure 3 Forest plot of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in FAS patients with severe dry eye disease



Notes: NVG06C103, SICCANOVE; NVG10E117, SANSIKA; FAS, Full analysis set

Source: company's response to clarification, figure A10.iii.1

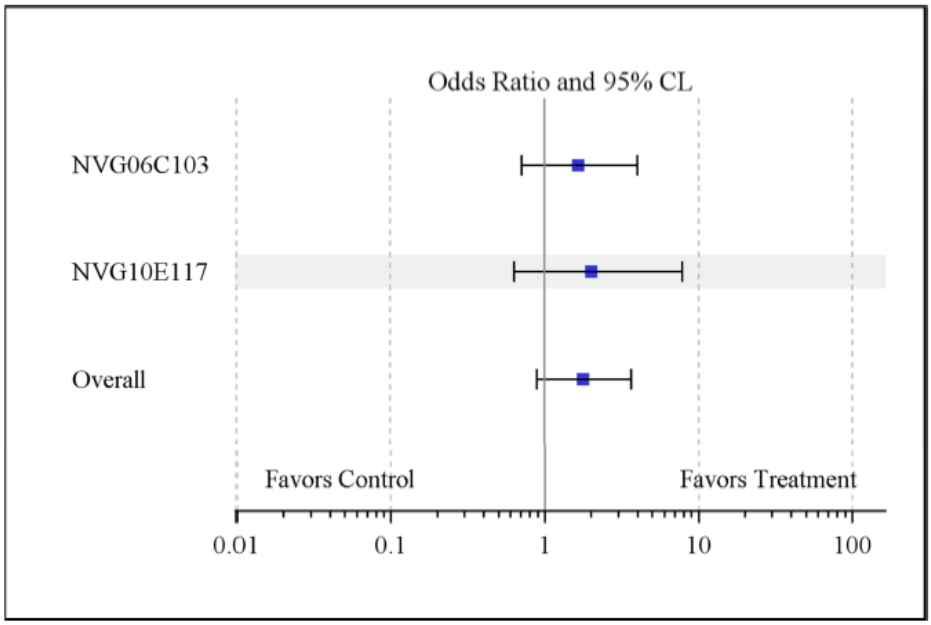
4.27 The company presented the results of the analysis of the composite end point CFS-OSDI response rate in people with Sjogren syndrome in SICCANOVE and SANSIKA and the results of a meta-analysis for this

using a fixed effects model. The results did not show any statistically significant difference between treatment groups in CFS-OSDI response in people with Sjogren syndrome (p=0.113) (see Table 9 and Figure 4).

Table 9 Meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in FAS patients with Sjogren syndrome

		Ciclosporin (n=146*)		**Vehicle (n=121*)**	
SANSIKA		**n**	**%**	**n**	**%**
	Responders	12	20.7	4	11.8
	Non-responders	46	79.3	30	88.2
	Total	58	100	34	100
SICCANOVE		**n**	**%**	**n**	**%**
	Responders	16	18.2	10	11.5
	Non-responders	72	81.8	77	88.5
	Total	88	100	87	100
SANSIKA + SICCANOVE		**n**	**%**	**n**	**%**
	Responders	28	19.2	14	11.6
	Non-responders	118	80.8	107	88.4
	Total	146	100	121	100
Logistic regression with Treatment Study Interaction p-value (Treatment)= 0.113 p-value (Study)= 0.796 p-value (Pooled country)= 0.926 p-value (Treatment Study interaction)= 0.794 Abbreviations: CFS, Corneal staining; OSDI, Oxford Surface Disease Index; FAS, full analysis set Source: adapted from table B14 in the company's submission and response to clarification question A10.i *N confirmed by the company to be correct					

Figure 4 Forest plot of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in FAS patients with Sjogren syndrome



Notes: NVG06C103, SICCANOVE; NVG10E117, SANSIKA; FAS, full analysis set

Source: company's submission, figure B4

4.28 The company also presented the meta-analysis results of SANSIKA and SICCANOVE for the composite end point CFS-OSDI response rate but only including people with Sjogren syndrome and severe dry eye disease. The results showed that the CFS-OSDI response rate at month 6 was statistically significantly higher with ciclosporin (23.4%) compared with vehicle (9.4%) (p=0.036*) (see Table 10 and Figure 5).

Table 10 Meta-analysis of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in FAS patients with Sjogren syndrome and severe dry eye disease

		Ciclosporin (n=77*)		**Vehicle (n=53*)**	
SANSIKA		**n**	**%**	**n**	**%**
	Responders	12	20.7	4	11.8
	Non-responders	46	79.3	30	88.2
	Total	58	100	34	100
SICCANOVE		**n**	**%**	**n**	**%**
	Responders	6	31.6	1	5.3
	Non-responders	13	68.4	18	94.7
	Total	19	100	19	100
SANSIKA + SICCANOVE		**n**	**%**	**n**	**%**
	Responders	18	23.4	5	9.4
	Non-responders	59	76.6	48	90.6
	Total	77	100	53	100

Logistic regression with Treatment Study Interaction

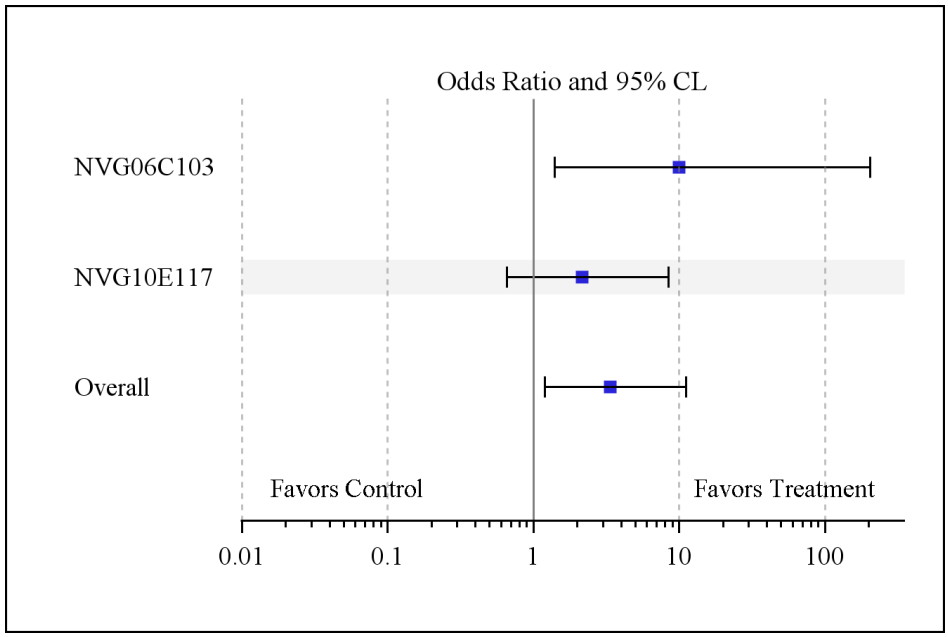
p-value (Treatment)= 0.036*
p-value (Study)= 0.987
p-value (Pooled country)= 0.650
p-value (Treatment Study interaction)= 0.288

Abbreviations: CFS, Corneal staining; OSDI, Oxford Surface Disease Index; FAS, full analysis set

Source: adapted from company's submission table B15

*p value taken from the draft EPAR and confirmed by the company to be correct
N confirmed by the company to be correct

Figure 5 Forest plot of SICCANOVE and SANSIKA for the composite end point CFS-OSDI at 6 months in FAS patients with Sjogren syndrome



Notes: NVG06C103, SICCANOVE; NVG10E117, SANSIKA; FAS, full analysis set

Source: company's response to clarification, figure A9.iv.1.

ERG comments

4.29 The ERG considered that only the meta-analyses for the subgroup of patients with Sjogren syndrome and severe dry eye disease are relevant to the decision problem.

Adverse effects of treatment

4.30 The company presented pooled adverse effects results from SANSIKA and SICCANOVE. It noted that this approach is justified because of the advantages of having a larger patient population which improves the precision of estimates, the administration dose was similar in both trials, the patient population was broadly comparable, the duration of the double-masked period was identical and the methodology to analyse adverse effects was comparable. The company explained that treatment-emergent adverse effects represent any event occurring after the baseline visits related or not to the study medication whereas treatment-related adverse effects represent an event considered by the investigator to be related to the study medication. The most frequent treatment-emergent

adverse effects with ciclosporin were instillation site pain, eye irritation, instillation site irritation and eye pain. The most frequent treatment-emergent adverse effects with vehicle were eye pain, meibomianitis (an inflammation of the meibomian glands, a group of sebaceous glands in the eyelids) and reduced visual acuity (for full details of adverse effects, see company's submission, table B21, page 134). In part 1 of SANSIKA, treatment-emergent adverse effects led to permanent stopping of treatment in a higher proportion of people having ciclosporin (11.7%; 29 events in 18 patients) compared with vehicle (6.7%; 8 events in 6 patients). When considering part 1 and part 2 of SANSIKA, 113 out of 154 patients (73.4%) had 275 treatment-emergent adverse effects. Approximately half these events (128 events) were considered by the investigator to be treatment-related. A total of 31 patients (20.1%) stopped treatment with ciclosporin over the 12 months because of a treatment-emergent adverse effect. The company concluded that the observed adverse effects of ciclosporin were mild to moderate and temporary and that overall ciclosporin is safe and well tolerated.

ERG comments

4.31 The ERG noted that the pooled adverse effects data for SICCANOVE and SANSIKA presented by the company included an estimate for the relative risk between treatment groups implying that statistical analyses were conducted. The ERG stated that although pooling adverse effects data is normally the preferred method for reporting the adverse effects results, only SANSIKA included people with severe dry eye disease exclusively and different vehicles were used in SANSIKA and SICCANOVE. It therefore considered the results of SANSIKA to be of greater importance for the appraisal. The ERG also noted that there were some differences in the rates of some adverse effects data between SANSIKA and SICCANOVE and considered that these differences may be because of the use of different vehicles or differences in disease severity between the 2 trials.

4.32 The ERG noted that the proportions of patients with the types of treatment-emergent adverse effects reported in SANSIKA were similar to those in the pooled analysis. It also noted that in SANSIKA, with the exception of severe ocular adverse effects and serious adverse effects, the proportion of adverse effects was greater in the ciclosporin group than in the vehicle group and that the proportion of adverse effects in people who only had ciclosporin was greater at 12 months than at 6 months. The ERG noted that based on the overall results only a minority of patients experienced treatment-related adverse effects and that there were mostly transitory and mild in severity and therefore it considered the safety profile of ciclosporin to be acceptable.

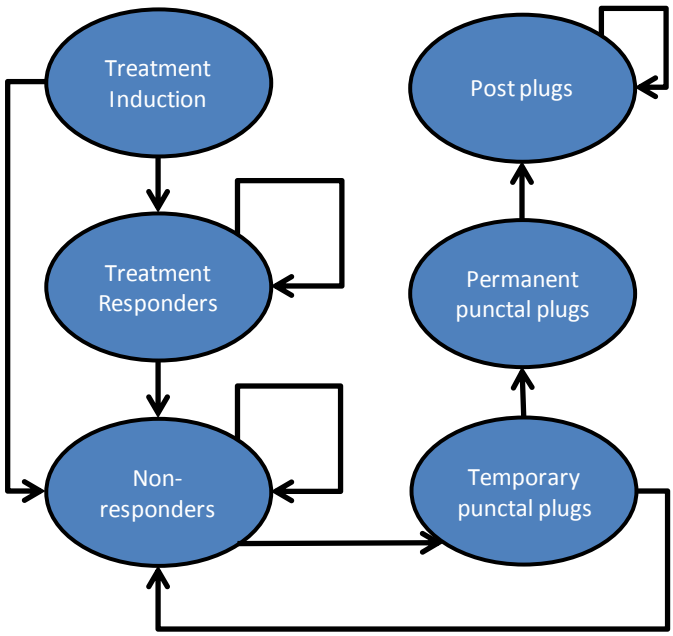
5 Cost-effectiveness evidence

Model structure

5.1 The company presented a de novo Markov economic model that assessed the cost effectiveness of ciclosporin compared with standard of care (artificial tears) in people over 18s with dry eye disease and severe keratitis whose disease has not adequately responded to tear substitutes. The company stated that the cost-effectiveness analysis was conducted from an NHS and Personal and Social Services perspective, costs and outcomes were discounted at 3.5% per year, the time horizon was 30 years and the cycle length was 3 months. The company noted that because people in SANSIKA represent the licensed population, inputs in the model were derived from this trial where possible. Because the comparator treatment in SANSIKA, vehicle, is not commercially available and artificial tears represent established clinical practice in the NHS for this population, the company viewed the response or reduction in the use of artificial tears in the vehicle group as a regression to the mean. The baseline use of artificial tears in SANSIKA was assumed to be reflective of standard care in the NHS.

5.2 The model included 7 different states including death (see Figure 6). People entered the model in the 'treatment induction' state where they have ciclosporin plus artificial tears or artificial tears alone for 6 months. People whose disease responds continue on treatment until it is no longer efficacious. When treatment is no longer efficacious, people move to the non-responders state. People stay in that state (receive artificial tears alone) or temporary punctal plugs are tried. If the disease responds to temporary punctal plugs they have permanent punctal plugs. People could die at any time in the model. Patients were assumed to be 61 years old and the model included equal number of men and women.

Figure 6 Company's model structure (excluding death)



Source: company's submission, figure B10, page 146

ERG comments

5.3 The ERG considered that results from SANSIKA cannot be used directly to inform an economic evaluation because the comparator (vehicle) is not commercially available and thus, cannot be considered established clinical practice in the NHS. The ERG suggested that the appropriate comparator for ciclosporin is other ciclosporin formulations. However,

because of lack of data it noted that the only valid economic comparison would be a cost-minimisation analysis assuming that all ciclosporin-based treatments have equivalent efficacy, similar adverse effects and have similar administration, prescribing and monitoring costs. The ERG considered that there is 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. It however provided further critique on the company's economic model but highlighted that this should not be understood to be any expression of support for the validity of the model or the results obtained from it.

5.4 The ERG noted that there were more women (85.3%) than men in SANSIKA and that the age range at baseline was wide (22 to 87 years). The ERG considered that it would be more appropriate to carry out modelling for each age – gender group combining the results to obtain a weighted average result. The ERG implemented this in scenario analyses (see scenario analysis 1 in section 5.19).

Model details

5.5 Treatment response was represented using the observed data from the post-hoc analysis of CFS-OSDI response rate from part 1 of SANSIKA (defined as improvement of 3 points or more from baseline in CFS in the analysed eye and improvement by 30% or more from baseline in OSDI). Response rates from the vehicle group were used to derive response rates for the artificial tears group in the model. People whose disease responded to the 6-month induction period continue treatment until there is no response. These response rates are derived from part 2 of SANSIKA. People who had vehicle in part 1 of SANSIKA and ciclosporin in part 2 were not included in the estimates for the model. The company assumed that transition probabilities were constant over time. The probability of stopping treatment with ciclosporin after 6 months (the end of SANSIKA) was taken from the rate of people stopping treatment with ciclosporin between 6 and 12 months in part 2 of SANSIKA. For the

artificial tears group, the rate of people who stopped treatment with vehicle during part 1 of SANSIKA was used as a proxy for the estimates after the end of the trial. The annual rate of temporary punctal plugs was assumed to be 0.01 based on a study by Clegg (2006) and only 10% of people who had temporary punctal plugs were assumed to subsequently have permanent punctal plugs. The response rate to permanent punctal plugs was assumed to be 100%. People who have temporary or permanent punctal plugs were assumed to not use artificial tears. Mortality rates were derived from the general population with 61 years, the mean age of people in SANSIKA. For details of the variables used in the company's model see Table 11.

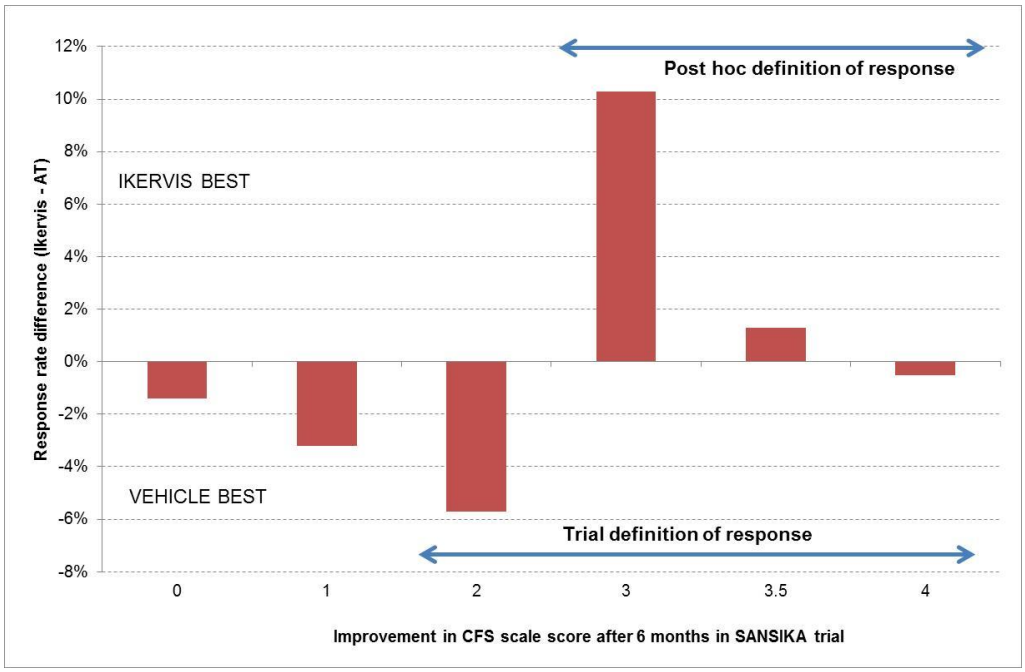
Table 11 Summary of efficacy inputs

Variable	Value	Standard Error
Ciclosporin 3 month response rate	0.162	0.016
Ciclosporin 6 month response rate	0.188	0.019
Vehicle 3 month response rate	0.077	0.008
Vehicle 6 month response rate	0.077	0.008
Non responder to temporary punctal occlusion transition probability	0.024	0.0002
Temporary to permanent punctal occlusion transition probability	0.1	0.01
Ciclosporin cycle failure probability	0.056	0.006
Vehicle cycle failure probability	0.063	0.006
Source: adapted from company's submission, table B26, page 158		

ERG comments

5.6 The ERG noted that the company used the post-hoc definition of CFS-OSDI response of SANSIKA which is more restrictive than the pre-specified one and states that this has a big impact on outcomes estimates and the cost-effectiveness results. It stated that the more restrictive definition excludes the level of benefit which most favours the vehicle group (see Figure 7).

Figure 7 Comparison of the relative response rate difference (ciclosporin – vehicle) across the range of possible CFS scores in SANSIKA at 6 months



Source: ERG report, figure 6, page 71

5.7 The ERG highlighted the population heterogeneity in the company's model. It noted that approximately 10% of people in SANSIKA were diagnosed no more than 2 years before randomisation and that there was no statistically significant difference in CFS-OSDI response from baseline at 6 months in the ciclosporin group using either the pre-specified (p=0.41) or the post-hoc definition of response (p=0.98). It however noted that people who had vehicle and were diagnosed no more than 2 years before randomisation showed CFS-OSDI response rates nearly double those showed by people having ciclosporin. The ERG cautioned that the number of patients was too small to derive definite conclusions but suggested that patients more recently diagnosed may be able to show short-term improvements in their condition delaying the need to have treatments such as ciclosporin.

5.8 The ERG considered that the company's assumptions about temporary and permanent punctal plugs are not robust because clinical advice to the

ERG suggested that response to punctal plugs surgery is not 100% and that artificial tears use would be reduced rather than eliminated.

5.9 The ERG noted that the company applied probabilities for continuing in treatment beyond the end of the trial from different time periods for each treatment group (6 to12 months for ciclosporin and 0 to 6 months for the vehicle) indicating lower discontinuation rates in the ciclosporin group (10.9%) compared with the vehicle group (12.2%). The ERG however noted that Kaplan-Meier analyses for stopping treatment in SANSIKA showed that there was a higher rate of stopping treatment in the ciclosporin group during the first month remaining stable thereafter (5.9% per 3 months) and that rates of stopping treatment were lower in the vehicle group with no evidence of any initial excess of people stopping treatment (4.6% per 3 months). The ERG explored applying these rates in scenario analyses and noted that this was its preferred option for modelling stopping treatment rates (see scenario 2 in section 5.19).

Resource use

5.10 The composition of preservative-free artificial tears was polyvinyl alcohol, carbomers and paraffin. The company assumed that administration, monitoring and testing costs with ciclosporin or artificial tears were zero because all treatments were self-administered and because it was assumed that the rate of ophthalmologist visits, tests and monitoring were similar in both treatment groups independently from the response status of the disease. It was assumed that people with severe dry eye disease have treatment in both eyes. The company assumed that the average number of drops per eye per day at baseline was similar in both treatment groups as per SANSIKA. The company incorporated the change in artificial tears use at 6 months to the ciclosporin and artificial tears groups in SANSIKA in the model noting that vehicle could have had an effect on the reduction of artificial tears use in the comparator group. For people whose disease did not respond to treatment, the number of artificial tears per eye per day was similar to this use at baseline. The company noted

that because treatment-related adverse effects were of low severity and transient, these were not included in the model other than through a reduction in the treatment continuation rates. The source of the costs for punctal plugs was NHS Reference Costs 2013. Unit costs were taken from the British National Formulary (month not stated). For a summary of treatment costs and assumptions related with resource use see Table 12.

Table 12 Summary of resource use

Variable	Value	Standard Error
Temporary punctal occlusion cost	£628.95	£62.89
Permanent punctal occlusion cost	£628.95	£62.89
Number of treated eyes	2	0.1
Polyvinyl alcohol usage	0.57	0.057
Carbomers usage	0.5	0.05
Paraffin usage	0.5	0.05
Ciclosporin cost per month	£72	
Average number of drops per eye per day at baseline and non-responders	14.89	
Cost of artificial tears use in non-responders per month	£88.63	
Average number of drops per eye per day at 6 month with ciclosporin (responders)	6.34	
Cost of artificial tears use in ciclosporin group per month	£38.67	
Average number of drops per eye per day at 6 month with artificial tears (responders)	7.32	
Cost of artificial tears use in artificial tears group per month	£44.40	
Source: adapted from company's submission, table B26, page 158; page 180; and table B39, page 182		

ERG comments

5.11 The ERG detected an inconsistency in the company's calculation of the frequency of artificial tears use at baseline and at 6 months. The ERG considered that no differences in artificial tears use between treatment

groups should be included in the model at baseline and at 6 months because neither of these differences was statistically significant. The ERG applied an average use of 6.83 drops per eye per day to both treatment groups in the model in scenario analyses (see scenario 5 in section 5.19).

5.12 The ERG also noted that the company applied treatment costs in the first 6 months assuming that treatment is prescribed for 3 months at the beginning of each cycle and considered that this does not take into account the small risk of patients dying or stopping treatment during a 3 month cycle. Based on clinical advice, the ERG assumed that treatment was prescribed monthly in scenario analyses. The ERG explored this in scenario analyses (see scenario 3 in section 5.19).

Utility values

5.13 The company used utility data from SANSIKA in the model. It noted that people whose disease responds need fewer artificial tears and have a higher utility which is assumed to be constant during response. People having punctal plugs have the same utility as people whose disease responds with ciclosporin or artificial tears (Table 13). In its sensitivity analysis the company applied utility values from Schiffman (2003) which derived utilities for people with different levels of severity of dry eye disease using the time trade-off method and adjusting for comorbidities.

Table 13 Summary of utility values

Variable	Value	Standard Error
No response utility	0.66	0.002
Change from baseline utility	0.08	0.03
Source: adapted from company's submission, table B26, page 158		

ERG comments

5.14 The ERG noted that the company's approach to modelling the utility values based on response is not influenced by treatment because EQ-5D results are pooled across both treatment groups. The ERG examined the EQ-5D results and noted that people in the vehicle group showed a larger

utility benefit based on response compared with people in the ciclosporin group (+0.038 using the trial definition of response, or +0.049 using the post-hoc definition). The ERG stated that pooling utility values in the model by response eliminates the potential impact of any differences because of treatment. The ERG considered that the most likely reason for the observed differences in utility values between treatments is that the additional adverse effects experienced by people having ciclosporin cause a reduction in the advantages derived from a response to treatment. The ERG investigated the effect of using separate trial utility values for each treatment group in scenario analyses (see scenario 4 in section 5.19).

Company's base-case results and sensitivity analysis

5.15 The company presented the results of its cost-effectiveness analysis for ciclosporin plus artificial tears compared with artificial tears alone in people with dry eye disease whose disease has not responded to artificial tears. The incremental cost-effectiveness ratio (ICER) of ciclosporin plus artificial tears compared with artificial tears was £19,156 per quality-adjusted life year (QALY) gained, with an associated incremental cost of £713 and 0.037 additional QALYs.

5.16 The company conducted deterministic and probabilistic sensitivity analyses. The variable that had the highest impact on the ICER was the utility value for responders. When varying the utility value for responders between 0.67 and 0.81 the ICER for ciclosporin plus artificial tears compared with artificial tears ranged from £165,654 to £10,166 per QALY gained. Other variables that had an impact on the ICER were the acquisition cost of ciclosporin and the response probabilities to ciclosporin and vehicle at 6 months (for full details of the company's deterministic sensitivity analyses see company's submission, table B46, page 193). The probabilistic analysis results gave an ICER of £18,835 per QALY gained for ciclosporin compared with artificial tears. The company noted that ciclosporin had a probability of 46.4% to be considered a cost-effective use of NHS resources at a maximum acceptable ICER of

£20,000 per QALY gained. It also noted that a number of simulations were associated with incremental benefits close to zero meaning that the probabilistic results should be interpreted with caution.

5.17 The company did not present a subgroup analysis for people with Sjogren syndrome and noted that SANSIKA was not powered to assess the benefit of ciclosporin in this subgroup and any inference would have needed using published literature in different patient groups or clinical input which would have added uncertainty to the model.

Company scenarios

5.18 The company presented several scenario analyses including:

- Scenario 1: using the primary end point definition for CFS-OSDI from SANSIKA (that is, improvement of 2 points or more from baseline in CFS and improvement by 30% or more from baseline in OSDI)
- Scenario 2: using utility values from Schiffman et al: 0.72 for non-responders and 0.78 for responders
- Scenario 3: varying the time horizon showing that the ICER increases above £20,000 per QALY gained when the time horizon is lower than 10 years
- Scenario 4: assuming that only 1 eye is treated.

The results of the scenario analyses are summarised in Table 14.

Table 14 Scenario analyses

Scenario	Inc. cost (£)	Inc. QALY	ICER (inc. cost per inc. QALY)
Base case	713	0.037	19,156
Scenario 1	1145	0.034	33,291
Scenario 2	713	0.029	24,765
Scenario 3	NR	NR	>20,000
Scenario 4	NR	NR	23,290
Abbreviations: Inc., incremental; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio; NR, not reported Source: company's submission, pages 194 – 198			

ERG exploratory analyses

5.19 The ERG corrected errors and applied different approaches in the company's model using both the pre-specified and the post-hoc CFS-OSDI response criteria from SANSIKA. The ERG re-emphasised that although it has attempted to explore the company's model, this should not be understood to be an expression of support of the validity of the company's model as stated in section 5.4. Cumulatively correcting the errors in terms of age-gender modelling (scenario 1, section 5.4), stopping treatment (scenario 2, section 5.9), treatment costs (scenario 3, section 5.12), responder utilities by treatment group (scenario 4, section 5.14), artificial tears use (scenario 5, section 5.11) and a small error in discounting (scenario 6) result in an ICER of £53,378 per QALY gained for ciclosporin plus artificial tears compared with vehicle plus artificial tears when the post-hoc CFS-OSDI response definition is used (see Table 15). When the pre-specified CFS-OSDI response definition is used, the cumulative impact of correcting all these errors result in ciclosporin being dominated by vehicle plus artificial tears (that is, ciclosporin plus artificial tears is more expensive and provides fewer QALYs than vehicle plus artificial tears) (see Table 16).

Table 15 ERG's exploratory analyses using the post-hoc CFS-OSDI definition of response from SANSIKA

Scenario	Ciclosporin + AT Total cost	Ciclosporin +AT Total QALY	Vehicle + AT total costs	Vehicle + AT total QALY	Inc. cost	Inc. QALY	ICER
Company's base case	£15,997	9.744	£15,283	9.707	£713	0.037	£19,156
ERG base case based on cumulative impact of below scenarios	£15,664	9.414	£4,735	9.397	£929	0.017	£53,378
Scenario 1	£15,238	9.277	£14,533	9.241	£705	0.036	£19,382
Scenario 2	£15,990	9.742	£15,245	9.713	£746	0.030	£25,020

Scenario 3	£16,181	9.744	£15,365	9.707	£816	0.037	£21,916
Scenario 4	£15,997	9.763	£15,283	9.733	£713	0.029	£24,473
Scenario 5	£16,038	9.744	£15,257	9.707	£780	0.037	£20,950
Scenario 6	£16,206	9.872	£15,483	9.834	£723	0.038	£19,153
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio, AT; artificial tears Source: ERG erratum, table 25							

Table 16 ERG's exploratory analyses using the trial CFS-OSDI definition of response from SANSIKA

Scenario	Ciclosporin + AT Total cost	Ciclosporin +AT Total QALY	Vehicle + AT total costs	Vehicle + AT total QALY	Inc. cost	Inc. QALY	ICER
Company's results	£16,132	9.788	£14,987	9.754	£1,145	0.034	£33,291
ERG base case based on cumulative impact of below scenarios	£15,786	9.406	£14,329	9.458	£1,457	-0.052	Dominated
Scenario 1	£15,370	9.320	£14,244	9.287	£1,126	0.033	£33,625
Scenario 2	£16,043	9.762	£14,987	9.754	£1,056	0.008	£133,290
Scenario 3	£16,293	9.788	£15,058	9.754	£1,235	0.034	£35,915
Scenario 4	£16,132	9.754	£14,987	9.782	£1,145	-0.027	Dominated
Scenario 5	£16,191	9.788	£14,942	9.754	£1,249	0.034	£36,307
Scenario 6	£16,343	9.916	£15,183	9.881	£1,160	0.035	£33,290
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio, AT; artificial tears Source: ERG erratum, table 25							

5.20 The ERG carried out an exploratory cost-minimisation analysis comparing ciclosporin with other pharmaceutical formulations of ciclosporin. The results showed that ciclosporin (Ikervis) is less costly than Restasis but more costly than other 2 ciclosporin formulations currently used in clinical practice in the NHS (see Table 17).

Table 17 Monthly costs of different ciclosporin formulations

Ciclosporin formulation	Monthly costs
Ciclosporin (Ikervis)	£72.00
Ciclosporin (Restasis 0.05% CsA drops)	£119.75
Ciclosporin (Optimmune 0.2% CsA ointment	£55.24
Ciclosporin (2% CsA drops)	£47.24
Abbreviations: CsA., ciclosporin Source: ERG report, page 64	

Innovation

5.21 Justifications for considering ciclosporin to be innovative:

- The company noted that ciclosporin is innovative in its potential to make a significant and substantial impact on health-related benefits for people with dry eye disease and severe keratitis who have a poor prognosis with no available authorised active treatments with demonstrated efficacy and safety
- It suggested that ciclosporin can be considered a 'step-change' based on its profile as an authorised treatment with a fixed formulation
- It noted that benefits in symptoms correlate poorly with objective clinical findings and are unlikely to be captured fully in the QALY calculation
- It also stated that the long term implications of a reduction in ocular surface inflammation and other objective improvements are unlikely to be captured in the QALY calculation, which currently assumes a conservative long-term benefit for people whose disease responds to both ciclosporin and artificial tears.
- It suggested that the benefit of administering 1 drop per day compared with, for example, a drop every 30 minutes needed with some artificial tears, is also unlikely to be included in the QALY calculation.

6 Equality issues

6.1 No equality issues were raised during the scoping process.

6.2 A professional group raised that if ciclosporin is not recommended by NICE in this guidance; a circumstance of postcode lottery may arise as the treatment (in the form of different pharmaceutical formulations) is currently being used in the UK.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

Clinical efficacy

The clinical trials program for Ikervis consisted of two phase II and two Phase III studies (see tabular overview in section 2.4.1.).

This application was based primarily on data from the pivotal Phase III SANSIKA study, a randomised, double masked, vehicle controlled multicentre European study that assessed Ikervis for the treatment of dry eye disease in patients with severe keratitis which did not improving despite treatment with tear substitutes. In addition, the applicant provided data from the supportive phase III SICCANOVE study in moderate to severe DED patients. The choice of the target population for the pivotal SANSIKA trial was based on post hoc results from SICCANOVE, which suggested a pronounced effect of Ikervis in the most severely affected patients [i.e. those with corneal fluorescein staining (CFS) =4 and Ocular Surface Disease Index (OSDI) ≥23].

The applicant furthermore provided the results of a meta-analysis of the 2 phase III studies (SANSIKA and severely affected patients in SICCANOVE).

Finally, supportive data was available from 2 phase II studies. In addition to informing the pharmacodynamic (PD), and safety profile of Ikervis in adult patients with DED, the 2 studies provided the rationale for dose selection for testing in Phase III. Relevant dose finding efficacy data from these studies are discussed in section 2.5.1.

In the absence of an appropriate active comparator, the applicant used Ikervis vehicle as a comparator in all studies. During the clinical development, the Ikervis formulation was changed with regards to the excipients. Benzalkonium chloride (BAK) was exchanged by cetalkonium chloride (CKC), both excipients being used as a cationic agent in the formulation to stabilise the oil-in-water emulsion. This change was prompted by the publication of the EMA Public Statement on Antimicrobial Preservatives in Ophthalmic Preparations for Human Use from 8 December 2009

(EMEA/622721/2009) to minimise the concentration of the quaternary ammonium compounds and related toxicity. One study in each Phase (II and III) was conducted with the BAK formulation and the CKC formulation. The formulation proposed for registration contains CKC and was used in the pivotal Phase III SANSIKA study.

Discussion on clinical efficacy

The clinical development programme of Ikervis consisted of 2 Phase III studies, the pivotal trial SANSIKA performed in severe DED patients and the supportive study SICCANOVE in moderate to severe DED patients, as well as two phase II studies. Furthermore, a meta-analysis of SANSIKA and SICCANOVE was performed, which was considered acceptable by the CHMP only in order to provide supportive and exploratory information to better estimate the magnitude of the treatment effect in particular with regards to the measurement of anti-inflammatory response (HLA-DR expression) and effect in patients with Sjögren syndrome.

The overall clinical programme was considered by the CHMP adequate to support the application for a marketing authorisation for Ikervis.

Design and conduct of clinical studies

The inclusion and exclusion criteria of the phase III studies were suitable to assure the integrity of the study and recruitment of a representative and well-defined population of DED patients, i.e. patients with DED symptoms and signs persisting despite the regular use of tear substitutes. The selection of severely affected patients for the pivotal SANSIKA study was reasonable, considering the outcome of a post-hoc analysis performed in patients with severe DED in the preceding SICCANOVE study, suggesting a greater response in this population.

Use of vehicle as a comparator is usually recommended for topical formulations and was therefore considered acceptable although it is well known that a vehicle has some beneficial effect by its own.

Signs and symptoms of DED were used as the primary endpoints, as co-variables (in the Phase III SICCANOVE supportive study) or in a composite responder variable in the pivotal Phase III SANSIKA study. These endpoints had been discussed and agreed with the CHMP as part of a scientific advice prior to this application.

Demographic and baseline disease characteristics were well balanced between the two treatment groups in both phase III studies. Both SANSIKA and SICCANOVE enrolled European patients who were generally representative of DED patients with respect to demographic and disease characteristics at baseline. As was expected, there were more female (≥80%) than male patients enrolled, with a mean age of 60 years or more, which was in line with data from large population-based epidemiological studies (DEWS report) for DED. Absence of data in children was acceptable as DED only very rarely occurs in the paediatric population and approval was only sought in adult patients.

Prior and concomitant study medications in SICCANOVE and SANSIKA studies were as expected for a DED population, balanced between the treatment groups, and similar in both studies; some patients had systemic corticosteroids, immunosuppressants including systemic ciclosporin (n=5, in SANSIKA study), beta-blockers, drugs known to be able to affect DED, but this was allowed by the study protocol since the dose remained stable throughout the study.

Efficacy data and additional analyses

- Dose selection

The dose of one drop ciclosporin 1mg/mL (0.1%) QD was chosen on the basis of non-clinical studies, as well as an early phase II study and was claimed by the applicant to have been asserted by optimal clinical effects in the SICCANOVE study. According to the applicant, the results from the phase IIa study N09F0502 showed a trend for improvement for the 0.1% BID group, but not for the 0.05% group. However, in the view of the CHMP, less convincing results were obtained from the Phase IIb ORA study, which showed a significant reduction in CFS of approximately 0.3 units for the 0.05% QD group relative to vehicle, whereas no reduction in CFS compared to vehicle was seen for the 0.01% strength. The applicant suggested that this might be a chance finding due to the small sample size and also pointed out that the study population in ORA consisted of mainly mild DED patients.

Taking into account all available information, the CHMP agreed that the 0.1% dose strength seemed to have shown the most consistent improvements. A BID dosing

was not expected to provide additional benefit, but may lead to compliance issues due to pain and irritation at site instillation.

- Clinical efficacy

The pivotal SANSIKA trial failed in its composite primary endpoint of DED sign and symptoms. The CFS-OSDI responder rate was 28.6% in the Ikervis 0.1% QD group and 23.1% in the vehicle group. The small difference in favour of Ikervis (5.5%) was not statistically significant.

With regards to the secondary endpoints, there was a statistically significant improvement in the CFS score over time in favour of Ikervis. A decrease of corneal staining was observed in both treatment groups at Month 6 compared to Baseline (-1.76 with Ikervis and -1.42 with vehicle). The observed difference of 0.35 units between active and vehicle arm appeared rather modest, but when translating the logarithmic scale into actual number of dots of staining, i.e. corneal lesions, the difference represents a ratio of 1.5 in the damaged surface area. This means that the vehicle group presented on average with 50% more dots/lesions compared to the Ikervis group, which was considered by the CHMP to be clinically meaningful. The CHMP had previously noted that normally an improvement by 1 step in the CFS score would be considered clinical relevant. This was not disputed by the applicant at the individual level and therefore responder analyses were performed. There was indeed a trend of a benefit of Ikervis over vehicle in pre-defined responder endpoints associated with corneal surface integrity, albeit statistical significance was not reached. The CFS responder rate (improvement of ≥2 grades) was higher in Ikervis patients with 51.9% versus 45.1% in the vehicle group and complete corneal clearing was achieved within 6 months of treatment for 6.5% of patients of the Ikervis group and for 4.4% of patients receiving vehicle. Furthermore, a number of post hoc analyses were performed and results were supportive of a benefit of Ikervis in improving corneal staining. When using a more stringent criterion for the CFS responder rate by increasing the required improvement from at least 2 grades to 3 grades, Ikervis was superior to vehicle at Month 6 ($p = 0.001$; 35.6% vs. 14.5%).

A statistically significant difference was furthermore observed in favour of Ikervis over vehicle in the reduction of HLA-DR expression measured using impression cytology. By Month 6, HLA-DR level of expression (AUF) remained elevated in the vehicle group, with a tendency to increase, while it had dropped substantially in the Ikervis group. HLA-DR is described in the scientific literature as one of the best evaluation standards of inflammation in the ocular surface and levels of HLA-DR have been shown to be elevated in patients with DED and in particular with Sjögren's syndrome. Treatment with Ikervis resulted in a reduction of these elevated levels to about 50,000 AUF, which may be considered a high level threshold of normal values. This level was maintained during the 6 months extension phase of the study, which supported a sustained anti-inflammatory effect of Ikervis. As inflammation is believed to be central to the cycle of events at the core of the mechanism of dry eye disease, being both a consequence as well as a mediator of DED, this finding was considered to be of relevance.

With regards to all other pre-defined endpoints (including OSDI, VAS, Schirmer test, use of concomitant artificial tears, investigator's global evaluation of efficacy, TBUT, lissamine green staining, quality of life score, and tear osmolarity), the SANSIKA study failed to show superiority of Ikervis versus vehicle including the pre-defined responder endpoints OSDI responder rate, VAS responder rate and CFS-VAS responder rate. Broadly consistent results were seen across all efficacy endpoints in that a general improvement was observed in both treatment groups over time compared to baseline. The OSDI score had improved by the end of part 1 of the study by -13.6 with Ikervis and -14.1 with vehicle. This improvement by itself can be considered clinically relevant, as the minimum clinically important difference for OSDI ranges from 4.5 to 7.3 for mild or moderate disease, and from 7.3 to 13.4 for severe disease (Miller 2010; Guillemin et al, 2012). Similar findings over time were shown for the VAS score, Schirmer test, TBUT, lissamine green staining, NEI-VFQ-25, EQ-5D and tear film osmolarity. There was also a progressive decrease in the use of artificial tears over time in both treatment groups, but the number of missing data was high and no between-group difference was seen.

Amongst the post-hoc analyses, tear film osmolarity in patients with an osmolarity level >308 mOsms/L at Baseline, a threshold known to be indicative of DED,

improved significantly more in patients treated with Ikervis than in the vehicle group (p=0.048). However, the CHMP noted the limited evidence that can be obtained from data derived post-hoc.

Globally, the results achieved during the first 6 months (part 1 of the SANSIKA study) were either maintained or improved further during the last 6 months (part 2).

With regards to the supportive phase III study SICCANOVE in moderate to severe DED patients preceding SANSIKA, the study also failed to demonstrate superiority of Ikervis over vehicle in the co-primary endpoint. A statistically significant treatment effect in favour of Ikervis was only observed for the co-variable of signs (change in CFS) while no difference between treatment groups was seen with regards to improvement in global ocular discomfort (VAS). A post-hoc analysis in the subgroup of patients with severe dry eye disease (CFS grade 4) at Baseline (n=85) showed a more pronounced effect of Ikervis including superiority of Ikervis over vehicle with regards to the percentage of co-responders on both signs (improvement of at least 2 grades in CFS) and symptoms (improvement of 30% OSDI score). In fact, based on this result, the applicant designed the SANSIKA study with the same patient population (severe DED) and using the co-responder endpoint from the post-hoc analysis as composite primary endpoint. It was therefore also not surprising that a meta-analysis of both phase III studies was able to show a statistically significant benefit of Ikervis over vehicle for the CFS-OSDI responder rate. Not only was this outcome driven by the CFS component of the endpoint, but by adding the subgroup of severe DED patients from SICCANOVE with a known pronounced effect for Ikervis to the patients in SANSIKA, the results of the meta-analysis were likely to be biased in favour of Ikervis.

When comparing the two studies, the CHMP noted that the vehicle response was substantially greater in SANSIKA compared to SICCANOVE. From the post hoc analysis in severely affected patients in SICCANOVE, an effect size of about 7% had been expected in the vehicle group for the CFS-OSDI responder rate. This could not be reproduced in SANSIKA where the treatment effect in the vehicle group was much higher with 23%. The applicant suggested that this might have been due to various factors, such as the heterogeneity and complexity of the disease, the poor

correlation between signs and symptoms, the choice of the responder definition, and the optimisation of the Ikervis formulation. While in SICCANOVE the former BAK formulation was used, the formulation in SANSIKA contained CKC as an excipient. The BAK formulation contained a higher concentration of quaternary ammonium compounds which might have caused ocular irritation. Whether this change contributed to the difference in the study findings was not clear. Furthermore, it could not be excluded with certainty that the ad libitum use of artificial tears in SANSIKA as opposed to the capped use of artificial tears allowed in SICCANOVE may have had an impact on the patients' subjective symptoms even with existing corneal erosion, which in turn might have confounded the results towards an increased effect size in patients in the vehicle arm in SANSIKA.

Post hoc subgroup analyses using data from both phase III trials suggested no relevant difference in any of the investigated subpopulations, including patients with Sjögren's syndrome. A general trend in favour of Ikervis could be seen.

Importantly, the phase III studies did not demonstrate a beneficial effect of Ikervis compared to vehicle on symptoms. This finding was complemented by the lack of a significant effect with regards to use of artificial tears and quality of life. However, in order to demonstrate efficacy in DED, generally a significant effect on both signs and symptoms or at least a significant effect in signs or symptoms and a strong trend for the other parameter would be preferred. The difficulty in establishing such combined effect was acknowledged by the CHMP as it was well known that signs and symptoms of DED poorly correlate and that some patients with a low degree of ocular surface damage experience severe symptoms, while others with substantial corneal lesions don't. One reason may be that advanced forms of DED with a high degree of ocular surface damage may cause reduced corneal sensation. Another reason could be a delay in the improvement of symptoms. Some support for a lag time effect on symptoms was provided by a post-hoc analysis presented by the applicant during an oral explanation. When testing the correlation (Spearman) between the change in CFS (signs) and OSDI (symptoms score) over time, the correlation increased slightly from month 1 through to month 6, thus suggesting that an improvement in signs may indeed with time result in an improvement in

symptoms. However, the correlation was overall weak and was considered inconclusive.

Following the suggestion that an effect on symptoms might only evolve over years, the CHMP recommended the conduct of a post-authorisation study to further explore long-term effects of Ikervis treatment on symptoms and disease complications. In order to ensure a suitable design, the CHMP furthermore recommended for the applicant to seek scientific advice on the study design.

Additional expert consultation

In the course of the procedure, the CHMP identified the need for expert input and thus an ad-hoc expert meeting was convened including also patient representative on the following questions:

Question 1.

In the treatment of severe dry eye disease (DED) (with severe corneal involvement), the experts are asked to comment on how a benefit of a medicine is best demonstrated considering effects on signs and symptoms of disease. Is an effect on signs of greater relevance than an effect on symptoms, and a sufficient basis upon which to approve a medicine alone?

The expert panel highlighted that DED is a multifactorial disease that, despite different possible triggers and aetiologies, is based on a common underlying vicious circle of factors including inflammation, which are inter-dependent and contribute to disease maintenance and progression. Both an improvement in signs and a relief in symptoms are important treatment objectives in DED. However, there is no clear correlation between signs and symptoms, in particular in severe forms of DED, where multiple factors including a potential loss in ocular surface sensitivity influence the symptomatology and so individual patients may suffer from pronounced pain and irritation while others experience less severe symptoms. As a result, it has proven difficult to demonstrate an effect of a medicinal product on both signs and symptoms and no such product is yet available. The clinicians also discussed that an improvement in signs could lead to a reduction of symptoms in the longer term

(possibly several years), once damaged cells and tissues had sufficient time to recover. However, such correlation has not been demonstrated to date.

The experts were of the view that in principle, an effect on signs only, if large enough, could be of clinical relevance in the context of a benefit-risk assessment, as it would help control the inflammatory process and disrupt the vicious disease cycle. Healing of the damaged ocular surface was an important treatment goal to prevent disease progression. However, the value of symptomatic relief for patients was not disputed. The patients confirmed that an improvement of symptoms was what they were looking for. In addition, a reduction in the use of artificial tears was considered by the patients of relevance.

Question 2.

Ikervis failed to show efficacy with regard to the primary endpoints in SANSIKA and SICCANOVE studies as there was no significant difference relative to vehicle, although there was demonstration of improvement in certain secondary endpoints and post-hoc analyses:

- Change in Corneal Fluorescein Staining (CFS) score using the Modified Oxford Scale: Over the 6-month treatment period in SANSIKA, a global effect of treatment in favour of Ikervis over vehicle was observed (p=0.017). At the end of Part 1 of the study (Month 6 Visit), the adjusted mean change in CFS score from baseline was -1.76 with Ikervis and -1.42 with vehicle (p=0.037), resulting in a between-treatment difference of 0.35.

- The decrease in HLA-DR level of expression (AUF) from baseline was greater with Ikervis than with vehicle, with a statistically significant difference at Month 1 (p=0.019) and Month 6 (p=0.021).

a. The experts are asked to comment on the clinical relevance of changes in CFS and HLA-DR (as compared to the vehicle effect) in the overall demonstration of a clinically relevant effect on DED.

b. Could the effect of Ikervis on corneal staining/keratitis translate into a role/contribution in avoiding serious and/or irreversible damage of the ocular surface including stromal defects and corneal ulcer development?

c. If so, what is the clinical relevance of the demonstrated effect?

d. Does a positive treatment effect in these two endpoints outweigh the absence of a treatment effect in the other endpoints studied (Ocular Surface Disease Index symptom score, ocular discomfort score, Schirmer test, use of concomitant artificial tears, investigator's global evaluation of efficacy, tear break-up time, lissamine green staining, quality of life score, and tear osmolarity)?

Question 2a.

With regards to the clinical relevance of the observed change in CFS, the experts considered the interpretation by the company, including the translation of the logarithmic CFS scale into number of stained dots on the ocular surface, which showed that a difference in CFS of 0.35 between Ikervis and vehicle corresponds to an average of 50% more dots with vehicle compared to Ikervis. During the discussion, some experts expressed their view that such interpretation including the excess rate and number needed to treat calculated for the responder analysis was sound and sufficiently convincing that the observed difference represents a clinically relevant benefit. The extend of ocular surface damage was considered related to functional outcomes (scattering of light) as well as predictive of disease progressions and complications. However, there was an opposing view expressed in that the difference was too small to be clinically meaningful in the overall clinical picture.

As for HLA-DR, it was agreed that it was widely used as an inflammation marker in epithelial cells and in some clinics HLA-DR expression is used to control the efficacy of anti-inflammatory drug treatment. However, it was not surprising that ciclosporin would reduce HLA-DR expression, as HLA-DR has previously been shown to form part of its immunomodulatory pathway. The applicant used this marker in line with a previous scientific advice obtained from the CHMP to confirm that an immunological effects on the ocular surface is achieved with Ikervis. Other inflammatory markers/signs were not investigated and one expert expressed the view that the

effect on HLA-DR alone, i.e. in the absence of a demonstrated effect for other inflammation markers/signs, was not sufficient to conclude on a meaningful anti-inflammatory effect of Ikervis. The other experts however considered the observed effect on HLA-DR to be of relevance and sufficient to assume an effect of Ikervis on inflammation.

Question 2b. and c.

There was agreement amongst the experts, that effective treatment of severe keratitis and repair of epithelial damage, as can be measured by corneal staining, can prevent serious complications in DED including pronounced and permanent damage of the ocular surface and function. However, the treatment effect would have to be sufficiently large to prevent worsening of the disease. In line with question 2a, the experts expressed different views on the relevance of the observed effects of Ikervis.

Question 2d.

The lack of a treatment effect in all but two pre-defined study endpoints (CFS and HLA-DR) was a concern for one expert who was of the view that the observed limited effects of Ikervis in CFS and HLA-DR were not sufficient to outweigh the failure in all other tested variables in particular with regards to the absence of a significant effect on symptoms, use of artificial tears and Quality of Life. However, it was proposed that ocular surface damage and inflammation (as measured by CFS and HLA-DR expression, respectively) may be factors at the beginning of a chain of relationships between all these variables, whereby effective treatment may result in immediate improvement of these two factors, but only in a delayed response within years for all others. Such mechanism could explain the study result and experts who had previously considered the observed effects to be of clinical relevance, maintained their view.

Question 3.

The experts are invited to discuss available treatment options for severe keratitis in patients with DED. In the experts' view, is there an unmet medical need in the treatment of severe DED that could be addressed with Ikervis?

The experts pointed out that treatment would depend on the aetiology of DED and ideally consists of an adequate control of the underlying disease. Apart from this, available treatments for DED include artificial tears/lubricants, which are effective in treating symptoms. Other therapeutic options commonly used in more severe forms of the disease include anti-inflammatory agents, i.e. corticosteroids for short-term use and topical ciclosporin (compounded or imported). Autologous serum was also considered beneficial.

None of the medicines used in clinical practice has a demonstrated effect on clinical signs of DED and many patients continue to express significant signs and suffer from impaired function as well as pain and irritation, requiring frequent use of artificial tears. Thus, there was consensus amongst the experts that there was an unmet medical need. This view was shared by the patients.

Some experts considered that Ikervis could help address this unmet medical need as it had shown a clinical relevant effect on signs and represented a valuable treatment option with limited side effects. However, one expert disagreed with this view and considered that a clinically relevant treatment effect has not been shown, in particular in absence of a demonstrated effect on symptoms and Quality of Life.

Conclusions on the clinical efficacy

Treatment with Ikervis resulted in an improvement compared to vehicle in the signs of DED as indicated by a reduction in the degree of corneal staining reflecting an improvement in corneal surface damage. The difference between treatments was moderate, but, taking into account the experts' view, the difference was considered by the CHMP clinically meaningful. Furthermore, Ikervis reduced ocular inflammation, which was considered of relevance as it may help disrupt the vicious disease cycle of DED. The lack of effect on symptoms explained largely why both phase III studies failed in their combined primary (co-primary or composite) endpoints.

Overall, the CHMP concluded that the available clinical data demonstrated an effect of Ikervis on the signs of DED, which by itself was clinically relevant as it helps control the inflammatory process and prevents disease progression. Thus, the available clinical evidence on efficacy was considered sufficient to support the application for Ikervis in the treatment of severe keratitis in adult patients with DED.

Benefit-risk balance

In light of the totality of the evidence and taking into account the experts' view, the CHMP concluded that the benefits of Ikervis outweighed its risks in the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes. Thus, the benefit-risk balance was considered favourable.

Discussion on the benefit-risk assessment

During the course of the procedure, the CHMP carefully considered the impact of the lack of a demonstrated effect of Ikervis on symptoms as well as for several other pre-defined endpoints compared to the observed effect in improving corneal surface damage and inflammation in the overall benefit-risk assessment. An ad-hoc expert group was convened to help explore the relevance of the benefits seen with Ikervis in the clinical development programme (see section 2.5.3. for details).

In summary, the experts considered alternative explanations for the lack of effect on symptoms and suggested that there might be a lag time whereby improvement in symptoms may occur only years after improvement in signs. With regards to the clinical relevance of the observed change in corneal staining, the experts considered the results sufficiently convincing and that the observed difference between Ikervis and vehicle represented a clinically relevant benefit. The extent of ocular surface damage was considered predictive of disease progressions and thus by improving the severity of keratitis, Ikervis may help to prevent serious complications. The effect on HLA-DR as an inflammation marker was considered by the experts to be of relevance and sufficient to assume an anti-inflammatory effect of Ikervis at the ocular surface, which could help to disrupt the vicious disease cycle of DED. Furthermore, while use of artificial tears has been shown to help improve symptoms in DED

patients, in the view of the experts there was no available treatment for DED at the time of this report with a demonstrated effect on signs.

During an oral explanation, the applicant further justified the clinical relevance of the benefits of Ikervis in the treatment of severe keratitis in patients with DED based on the improvement of ocular surface damage (reduced CFS) and the anti-inflammatory effect (reduced HLA-DR expression). The applicant pointed out that significantly more patients had a pronounced improvement in the CFS grade from grade 4 at baseline to at least grade 1 compared to vehicle, although this analysis was only done post-hoc.

Overall, taking into account the experts' view, the CHMP concluded that the available clinical data had shown a relevant treatment effect of Ikervis, that, even in absence of an effect on symptoms, by itself was clinically meaningful. The CHMP was of the view that the initially proposed indication should be changed from treatment of DED in adult patients with severe keratitis to treatment of severe keratitis in adult patients with dry eye disease, as the latter was considered to be more in line with the demonstrated treatment effect on signs. In this population, Ikervis was considered to represent a valuable treatment option with limited side effects.

Following the suggestion by the experts that an effect on symptoms might only evolve over years, the CHMP recommended the conduct of a post-authorisation study to further explore long-term effects of Ikervis treatment on symptoms and disease complications. The CHMP furthermore recommended for the applicant to seek scientific advice on the protocol for this study to ensure a suitable study design. The CHMP furthermore recommended that the applicant pursued the proposal for the conduct of a non-clinical post-approval study to explore drug-drug interactions at receptor and at the cellular level.

Finally, the CHMP discussed the rationale for the dosing used in the phase III trials and while there were conflicting results from type II studies, overall, the 0.1% dose strength seemed to have shown the most consistent improvements while being well

tolerated. No advantage of BID dosing compared to QD dosing was expected and thus, the CHMP endorsed the dose recommendations.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Ikervis in the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the Marketing Authorisation

- Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.

Divergent Position

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of a Marketing Authorisation for Ikervis for the treatment of severe keratitis in adult patients with dry eye disease (DED), which has not improved despite treatment with tear substitutes.

The reason for the divergent opinion was as follows:

The hypothesis generated by the study SICCANOVE (i.e. Ikervis worked better in the more severe DED patients) was not confirmed by the pivotal trial (SANSIKA). Ikervis failed to show efficacy with regard to the primary endpoints (combined signs and symptoms) as there was no significant difference relative to vehicle. The clinical relevance of the limited improvement in certain secondary endpoints and in post-hoc analyses are considered highly questionable. Thus, considering that efficacy has not been convincingly shown, the benefit-risk balance is considered to be negative.