STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ciclosporin for treating dry eye disease

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Dwan K	Critical appraisal of the statistical evidence
Kotas E	Cross checking of the submission search strategy
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Ahmad S	Clinical advice and critical appraisal of the clinical sections of the company's submission

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

AEs	Adverse events
AT	Artificial tears
AUF	Arbitrary Units of Fluorescence
BAK	Benzalkonium chloride
CEAC	Cost effectiveness acceptability curve
CFS	Corneal fluorescein staining
CHMP	Committee for Medicinal Products for Human Use
CKC	Cetalkonium chloride
CS	Company's submission
CsA	Ciclosporin
CSR	Clinical study report
DED	Dry eye disease
CSR	Clinical study report
DEWS	Dry Eye Workshop
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
FAS	Full analysis set
HLA-DR	Human leukocyte antigens DR
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ITT	Intention-to-treat
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NICE	National Institute for Health and Care Excellence
OSDI	Ocular Surface Disease Index
PSA	Probability sensitivity analysis
QALY	Quality adjusted life year
OSDI	Ocular Surface Disease Index
RCT	Randomised controlled trial
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
STA	Single technology assessment
TBUT	Tear film break up time
VAS	Visual analogue scale

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE by Santen GmbH in support of the use of ciclosporin (CsA) 0.1% (Ikervis) for the treatment of dry eye disease (DED) and severe keratitis which has not improved despite treatment with tear substitutes. Tear substitutes include artificial tears (AT).

Ikervis is not currently licensed for use in Europe but received a positive opinion from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) on 22 January 2015. The expected marketing indication is for patients with DED and severe keratitis which has not improved despite treatment with tear substitutes.

1.1 Critique of the decision problem in the company's submission

The population identified in the NICE decision problem is "people with severe DED (DEWS 3 or 4) whose disease has not adequately responded to tear substitutes". The population described by the company in its decision problem is patients with DED and severe keratitis which has not improved despite treatment with tear substitutes. The term "severe DED" used by the company in the pivotal SANSIKA trial is defined using signs (corneal fluorescein staining [CFS] = 4, Schirmer's test without anaesthesia ≥ 2 mm/5 min and <10 mm/5 min) and symptoms (Ocular Surface Disease Index [OSDI] ≥ 23). This definition is not identical to that specified in the scope using DEWS. However, although DEWS are one set of criteria for measuring severe DED, criteria for defining severe DED vary between geographical areas and healthcare professionals in clinical practice.

The intervention specified in the NICE scope and described in the company's decision problem is CsA. However, the intervention specifically being addressed by the company (and for which marketing authorisation and a NICE recommendation is being sought) is Ikervis, CsA 0.1% with cetalkonium chloride (CKC) as an excipient.

The following comparator is specified in the NICE scope and in the company's decision problem: standard treatment for DED without CsA (such as AT, eye ointments and acute use of topical corticosteroids). However, the comparator in the trial evidence presented by the company is the Ikervis vehicle, a sterile, drug-free, cationic ophthalmic emulsion containing no CsA and which is not available commercially. The company argues it cannot be regarded as a placebo as it is considered to offer some therapeutic benefit. Indeed, it is noted that the

company has previously described the vehicle to be similar to Cationorm ocular lubricant which has demonstrated efficacy compared to eye drops and is used in some countries (but not in the UK). The comparator in the economic analysis conducted by the company is considered to be AT.

Expert advice to the ERG suggests that there are a number of formulations containing CsA that are currently used in UK clinical practice including CsA 0.05% (Restasis), CsA 2% eye drops and CsA 0.2% ointment (Optimmune). The ERG considers that these formulations are also appropriate comparators. Unfortunately, however, there is insufficient clinical evidence to allow a direct, or an indirect, comparison between Ikervis and any of these formulations to be carried out.

The clinical outcomes presented by the company are similar to those specified in the NICE scope. In addition, the company's cost effectiveness analysis has been carried out in line with the specifications in the NICE scope (quality adjusted life years [QALYs], NHS perspective and lifetime horizon). In terms of subgroup analyses, the NICE scope states that an analysis of people with Sjögren's syndrome should be considered. The company carried out a clinical effectiveness comparison for this subgroup based on pooled data from the SANSIKA trial and a subgroup of patients defined as having severe DED in the supportive SICCANOVE trial (CFS = 4 and OSDI ≥ 23). It was considered that there was an insufficient number of patients with Sjögren's syndrome in the SANSIKA trial to allow a cost effectiveness analysis to be undertaken.

1.2 Summary of clinical effectiveness evidence submitted by the company

Clinical evidence is presented from two company sponsored phase III randomised controlled trials (RCTs): SANSIKA (N = 246) and SICCANOVE (N = 496). The former is considered pivotal because it only includes patients with severe DED (CFS = 4, Schirmer's test without anaesthesia ≥ 2 mm/5 min and <10 mm/5 min OSDI ≥ 23), whilst the latter is considered to be supportive as it includes a broader population, defined as those with moderate to severe DED (defined using CFS = 2 and a number of other measures of signs and a visual analogue scale [VAS] for symptoms, rather than OSDI). The vehicle in SANSIKA contained CKC and that in SICCANOVE contained benzalkonium chloride (BAK). Post-hoc efficacy analyses were conducted in participants in the SICCANOVE trial with severe DED. Two different definitions of severe DED were used in SICCANOVE: (i) CFS = 4 (n = 85 [17%]) and (ii) CFS ≥ 3 and OSDI ≥ 23 (n = 246 [50%]). Both trials compared Ikervis to its vehicle the formulation of which, as noted above, was different in each trial.

Results from the SANSIKA trial show that there is no statistically significant difference between arms for the primary outcome, which was a composite endpoint of signs and symptoms (CFS-OSDI) as measured by a ≥ 2 improvement in CFS and a 30% improvement in the OSDI. However, statistically significant differences were reported for the following pre-specified outcomes that measure signs: changes in CFS and human leukocyte antigens DR (HLA-DR) expressions on the conjunctival cell surface (quantified in Arbitrary Units of Fluorescence [AUF]). Statistically significant differences between arms were also reported for outcomes analysed post-hoc: CFS improvements ≥ 3, worst tear-film osmolarity (but only in patients with elevated tear film osmolarity at baseline) and a more stringent definition of the composite CFS-OSDI responder rate (CFS improvement ≥ 3 and OSDI improvement ≥ 30%). There were no statistically significant differences between arms for health-related quality of life (HRQoL) measured by the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) or European Quality of Life-5 Dimensions (EQ-5D).

Results from the SICCANOVE trial in patients with moderate to severe DED, show a statistically significant difference in change in CFS but not in change in global ocular discomfort measured by a VAS, the co-primary endpoints. Post-hoc analyses in a severe population identified statistically significant differences between arms for a number of outcomes measuring signs and also for CFS-OSDI response defined as CFS improvement ≥ 2 and OSDI improvement ≥ 30%.

In patients with Sjögren's syndrome and with severe DED (CFS = 4 and OSDI ≥ 23, n = 130), pooled data from SANSIKA and SICCANOVE were presented for the rate of CFS-OSDI responders (patients with an improved CFS ≥ 2 and an improved OSDI ≥ 30%). Response was statistically significantly higher for Ikervis than vehicle (23.4% versus 9.4%; p = 0.028).

Adverse events (AEs) in both trials were more common in those treated with Ikervis than in those receiving the respective vehicles. In the SANSIKA trial, treatment-related ocular AEs were reported by 37.0% of patients treated with Ikervis compared to 20.0% of those in the vehicle arm (in patients who had received Ikervis for 12 months the proportion was 45.5%). The majority of AEs occurred at the time the drops were put into the eye.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is satisfied with the search strategy employed by the company to identify clinical effectiveness studies, and is reasonably confident that all relevant studies were identified and included in the review.

The ERG considers that, for two reasons, evidence from the SANSIKA trial is more relevant to the decision problem than evidence from the SICCANOVE trial. First, the whole SANSIKA trial population has severe DED but only a (non-randomised) sample of those recruited to the SICCANOVE trial has severe DED (17% or 50% of the population depending on the definition used). Second, the vehicle used in the SANSIKA trial is the proposed licensed Ikervis formulation (containing CKC), whereas the vehicle used in the SICCANOVE contained BAK.

With the exception of change in CFS, the ERG notes that none of the statistically significant differences between Ikervis and vehicle found from post-hoc analyses of SICCANOVE trial data were also found from analysis of SANSIKA trial data. Importantly, the primary outcome (CFS-OSDI) showed no statistically significant difference and so the relative clinical effectiveness of Ikervis compared to vehicle was not demonstrated. However, the ERG questions the relevance of this outcome for two reasons. First, it is not clear if the concept of a response formally defined by specific changes in only CFS and OSDI is clinically meaningful. Second, if it is accepted that the concept of response is clinically meaningful, then the issue is the lack of evidence available to support the use of any specified threshold value for this measure. The ERG is, therefore, unable to comment on whether the CFS-OSDI response as defined in SANSIKA (CFS improvement ≥ 2 and OSDI improvement ≥ 23) or the CFS-OSDI response defined post-hoc (also using data from SANSIKA) and used to inform the economic model base case (CFS improvement ≥ 3 and OSDI improvement ≥ 23), is most appropriate.

The ERG notes that the rates of eye irritation, eye pain and site irritation were higher in the SICCANOVE trial than in the SANSIKA trial; whilst rates of site pain were higher in the SANSIKA trial than in the SICCANOVE trial. However, overall, only a minority of patients experienced treatment-related AEs. These were mostly transitory and mild in severity and therefore the safety profile appears to be acceptable.

The ERG considers that the value of the evidence from the SANSIKA trial is limited by the fact that it uses the Ikervis vehicle as the comparator intervention, rather than any of the comparators specified in the NICE scope. Not only is the vehicle not commercially available, it is not currently used in routine clinical practice; in addition, the company argues that it may offer some therapeutic benefit. Certainly, improvements over time were reported for all efficacy outcomes in the vehicle arm of the SANSIKA trial. However, it is not clear whether the improvements occurred as a result of the vehicle, as a result of concomitant AT use, or as a combination of both vehicle and AT.

While a comparison of Ikervis with this vehicle was considered by the EMA CHMP and the company to be valid, the ERG considers that a comparison of Ikervis with other CsA formulations would have been more informative. It was not possible, however, to make such comparisons directly, or to conduct a formal indirect treatment comparison due to the lack of a common comparator. A very crude (non-statistical) comparison, undertaken by the ERG, of evidence reported in a standalone systematic review report, suggests that Ikervis compares favourably with Restasis in terms of changes in CFS and OSDI, while AEs may be more common in patients treated with Ikervis. However, the ERG stresses that these comparisons are crude and the suggested conclusions should be treated with caution.

1.4 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo state transition (Markov) model to compare Ikervis plus AT with AT alone. The model comprises six health states: treatment induction, treatment responders, non-responders, temporary punctal plugs, permanent punctal occlusion and post plugs. It has been developed in Microsoft Excel using a 3-monthly cycle length. It includes a half-cycle correction and the time horizon is set at 30 years. As recommended by NICE, a discount rate of 3.5% has been used for both costs and outcomes; outcomes are measured in QALYs. The model perspective is that of the UK NHS. Resource use, costs and utilities are mainly based on information from the SANSIKA trial with efficacy (and associated utility) of AT being assumed to be equivalent to that of the vehicle arm of that study. Other resource use and cost information have been extracted from published sources.

The company's base case analysis uses efficacy results generated when the post-hoc definition of response (CFS ≥ 3 and OSDI ≥ 30%) was applied. For the comparison of Ikervis plus AT versus AT, the company's incremental cost-effectiveness ratio (ICER) per QALY gained is £19,156. The company carried out a wide range of deterministic sensitivity analyses. The results show that the most influential variable is response utility which, when the lower value (two standard errors below the mean) was used, increased the ICER per QALY gained to £165,654. None of the other deterministic sensitivity analyses resulted in an ICER above £30,000 per QALY gained. The results of the company's probabilistic sensitivity analysis (PSA) show that, compared with AT alone, the probability of Ikervis plus AT being cost effective is 46.4% at a threshold of £20,000 per QALY gained and 70.7% at a threshold of £30,000 per QALY gained. It should be noted, however, that a scenario analysis, that used efficacy results generated when the pre-specified primary endpoint criteria in the SANSIKA trial (CFS ≥ 2 and OSDI ≥ 30%) were applied, resulted in an ICER of £33,291 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is satisfied with the search strategy employed by the company to identify cost effectiveness studies, and is reasonably confident that no relevant published articles exist.

The ERG does not consider that the evidence available is sufficient to support a valid cost effectiveness analysis of Ikervis versus currently prescribed UK treatment options for severe DED. The economic model compares Ikervis plus AT versus AT and the model is largely populated with data from the SANSIKA trial. The results of the SANSIKA trial cannot be used directly in the model as the Ikervis vehicle is not a placebo, nor is it currently used in clinical practice. Instead, the company has made the assumption that the Ikervis vehicle and AT have the same efficacy.

The ERG has identified a number of issues relating to the data used to populate the model and/or how the data have been implemented. First, the model base case uses results from an analysis based on a post-hoc alteration to the primary outcome (i.e. ≥ 3 improvement in CFS and a 30% improvement in the OSDI). This leads to a more favourable ICER per QALY gained for Ikervis than if the pre-specified definition of the primary outcome had been used (≥ 2 improvement in CFS and a 30% improvement in the OSDI).

Second, the SANSIKA clinical study report (CSR) shows that trial discontinuations for any reason (16.2% versus 12.2%) are higher in the Ikervis group compared with those receiving vehicle. The company modellers have applied treatment costs in the first 6 months (i.e. the trial period) assuming that treatment is prescribed for 3 months at the beginning of each cycle. However, this takes no account of the small risk of patients dying or discontinuing treatment during a 3 month cycle.

Third, the company approach to modelling the utility effect of response to treatment is based on an assumption that improvement in HRQoL is not influenced by the treatment given and so HRQoL data are pooled across both arms of the SANSIKA trial. However, examination of the trial results indicates that a larger utility benefit is received by patients responding to treatment with vehicle than those who respond to Ikervis treatment. The effect of using the pooled utility results in the model is to eliminate the potential impact of any differences in patient experience due to the characteristics of the randomised treatment.

Other issues identified by the ERG are: incorrect AT usage calculations, incorrect discounting, naïve and inaccurate modelling of the age/sex profile of patients and insufficient variation in the trial outcome parameter values used in the PSA. In addition, the ERG has

detected model coding errors relating to the number of patients alive at the beginning of each model cycle. The ERG has not been able to correct these coding errors in the time available and it is not clear how they impact on cost effectiveness results.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical evidence

- The trials from which clinical evidence are derived appear to be at low risk of bias and measure efficacy in terms of signs and symptoms, AEs and HRQoL, all of which are important outcomes to clinicians and patients. The trials also appear to be generalisable to clinical practice in England in terms of patient characteristics.
- Only a minority of patients treated with Ikervis reported treatment-related AEs and these were mostly mild and transitory.

Cost effectiveness evidence

- The company supported the appraisal process by providing all of the additional analyses requested by the ERG in a timely manner.

1.6.2 Weaknesses and areas of uncertainty

Clinical evidence

- The company presents evidence from two trials, SANSIKA and SICCANOVE. However, the evidence presented in SICCANOVE is largely irrelevant to the decision problem as a maximum of 17% of its population have severe DED (as per the definition used in the SANSIKA trial) and because the company is not seeking a recommendation for CsA with the vehicle (containing BAK) used in the trial.
- The primary outcome was not met in the SANSIKA trial and so, notwithstanding the ERG's uncertainties as to the relevance of the primary outcome used, the superiority of Ikervis has not been demonstrated in patients with severe DED.
- The comparator arm of the SANSIKA trial (vehicle) is not used in clinical practice but cannot be regarded as a placebo as it is argued by the company that it offers some therapeutic benefit. It is, therefore, unclear if improvements in efficacy reported over time in the vehicle arm are a result of the vehicle, AT, or a combination of both.
- The SANSIKA and SICCONOVE trial vehicles contain different excipients and it is unclear whether they can be considered comparable, particularly as AE profiles differ (rates of eye irritation, eye pain, site irritation and site pain and rates of AE severity).
- No comparison is made (or can be made, due to lack of available evidence) between Ikervis and other CsA-containing formulations that are currently used in UK clinical practice.
- The results of the pivotal SANSIKA trial showed no statistically significant improvements in symptoms for patients receiving Ikervis compared with those receiving vehicle and, of the pre-specified outcomes measuring signs, only a change in CFS and HLA-DR expressions on the conjunctival cell surface (HLA-DR) were statistically significant.

Cost effectiveness evidence

- The ERG does not consider that the evidence available is sufficient to support a valid cost effectiveness analysis.
- The company's model assumes that AT and vehicle have the same efficacy, an assumption that may be overly conservative if vehicle does have a therapeutic effect over and above that of AT alone.
- The model base case uses results from an analysis based on a post-hoc alteration to the primary outcome. The ERG notes that using these figures generates results that are more favourable to Ikervis than if results based on the pre-specified definition of the primary outcome had been used.
- In addition, the ERG has identified modelling issues relating to age/sex profile, treatment discontinuation, treatment costs, responder utility, AT usage and discounting.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

In the absence of clinical evidence allowing a comparison between Ikervis and any of the other CsA formulations that are used in current clinical practice in England, the ERG carried out a cost minimisation analysis. This assumes that all CsA based treatments are of equivalent efficacy, are associated with similar AEs and incur similar administration, prescribing and monitoring costs. The ERG acknowledges that such an assumption is open to criticism. The results of this analysis show that Ikervis is less costly than Restasis (0.05% CsA drops) but more costly when compared with other CsA formulations currently used (off-label) in clinical practice (Optimmune [0.2% CsA ointment] and 2% CsA drops).

The ERG does not consider that the evidence available is sufficient to support a valid cost effectiveness analysis of Ikervis versus currently prescribed UK treatment options for severe DED. Furthermore, the ERG has identified a number of issues that limit the credibility of the company's model. To address these issues the ERG has, where possible, carried out modifications to the model. However, **results from the ERG's analyses should not be understood to be any expression of support for the validity of the model or the results obtained from it**.

The ERG considers that the company model can only generate cost effectiveness results for the comparison of Ikervis plus AT versus vehicle plus AT. The ERG implemented six specific model changes using the ERG's preferred alternative parameter values were in relation to age/sex modelling, treatment discontinuation, treatment costs, responder utility, AT use and discounting. The impact of each of these changes on the company's base case (which utilises the post-hoc definition of response in the SANSIKA trial) leads to changes in the ICER per QALY gained for the comparison of Ikervis plus AT with vehicle plus AT that range

from -£2 to + £5,864. If all of the ERG amendments are applied, the ICER per QALY gained increases from £19,156 (company's estimate) to £53,253.

The ERG's changes to the alternative base case (which utilises the pre-specified SANSIKA trial definition of the primary outcome) lead to changes in the ICER per QALY gained for the comparison of Ikervis plus AT with vehicle plus AT that range from Ikervis being dominated to an increase in the ICER of + £99,999. If all of the ERG amendments are applied then Ikervis plus AT is dominated by vehicle plus AT, i.e. treatment with vehicle plus AT generates more utility gain than treatment with Ikervis plus AT.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 2.1 of the CS provides a brief overview of DED. Sections 2.1, 2.2 and 8.1 provide data on the number of patients with DED, and section 2.3 provides details about life expectancy of people with DED in England and Wales. These sections appear to appropriately present the key issues relating to the underlying health problems of patients with DED and key points from the CS are in Box 1. In particular, the ERG notes the company's assertion that signs and symptoms of DED are poorly correlated (the ERG notes a recent publication[1] cites a study reporting this poor correlation in up to 40% of patients[2]). One consequence of this is that accurate estimates of incidence and prevalence of severe DED are difficult to determine. The ERG further notes that although there is no evidence that DED impacts on life expectancy, it appears to impact on quality of life.

Box 1 Company's description of dry eye disease and epidemiology

Dry eye disease (DED)

- DED is a multifactorial, chronic and progressive ophthalmic disease causing inflammation and damage to the ocular surface with increased osmolarity of the tear film [3,4]
- DED is a disorder of the lacrimal glands, the entire ocular surface (cornea, conjunctiva and meibomian glands), and the eye lids, as well as the sensory and motor nerves that connect them[5]
- Symptoms of DED include discomfort, visual morbidity or disturbance and tear film instability with potential damage to the ocular surface[3,6]
- DED is usually chronic, and no specific cure exists
- Complications associated with DED include conjunctivitis, corneal ulceration, and corneal infection[7]
- DED may also compromise results of corneal, cataract or refractive surgery[8]
- DED prognosis shows considerable variance, depending upon disease severity as well as the severity of the underlying pathology
- Once DED has developed, inflammation becomes the key mechanism of injury to the entire ocular surface (the adnexa, conjunctiva and cornea[9-11]
- DED severity is commonly assessed using subjective questionnaires, in conjunction with objective invasive and non-invasive assessments. The choice of assessment varies between jurisdictions and physicians
- There is no evidence that DED impacts life expectancy

Epidemiology

- The overall prevalence of DED in the literature (all severities) varies widely, between 0.1%-27% in the USA, Australia, and Europe[12-14] depending on the elicitation methods and diagnostic criteria used
- There are no reports of the prevalence of severe DED in England, Wales, or in the UK in general
- When assessing the epidemiology of dry eye, it is important to take into account risk factors for developing the condition. Besides incidental risk factors like smoking or air-conditioning, age and female sex are the most relevant systemic risk factors for dry eye disease when assessing the overall prevalence
- In order to assess the share of patients that can be regarded as severe, it is important to acknowledge that neither subjective symptoms nor objective signs alone allow for an accurate estimate, because they poorly correlate in this condition[15]

Source: Sections 2.1, 2.2, 2.3 and 8.1 of the CS

As noted in Box 1, different measures are used to assess severity of DED. In the UK, signs of DED are conventionally measured by CFS and tear film break up time (TBUT); Schirmer's tear test, lissamine green staining and tear film osmolarity may also be used. The ERG highlights a recent publication[1] by the ODISSEY European Consensus Group which has assessed 14 commonly used criteria used to determine severe DED. The authors concluded that a CFS score ≥ 3 on the Oxford scale and OSDI score ≥ 33 were enough to clearly establish a diagnosis of severe DED in those patients whose signs and symptoms of disease associate well. However, as noted above and in Box 1, signs and symptoms of DED are sometimes poorly correlated. Hence when there is discordance between signs and symptoms measured only using CFS and OSDI, they recommend that further additional evaluations (e.g. Schirmer's tear test) are needed in order to improve diagnostic specificity. The authors of this paper[1] recognise that their criteria are based on a consensus based approach and are therefore not strictly evidence-based. Therefore they hope to test the validity of the ODISSEY scoring algorithm in the context of clinical trials.

The company notes there are no UK estimates for the prevalence of severe DED. However, Vehof et al 2013[13] has determined the prevalence of DED of any severity using data from a population-based cross-sectional study of 1635 female twin volunteers (the TwinsUK adult registry[16]). A number of different criteria for measuring DED was used and results suggest that the prevalence of DED lies somewhere between 13.4% and 31.5% (Table 1).

Table 1 Estimates for the prevalence of DED in UK twins (median age of 60 years)

Criteria for defining DED*	Proportion (%)
All subjects (N = 1,635)	
DED diagnosis by physician	13.4
Use of artificial tears	16.2
DED symptoms past 3 months	21.7
Any of above 3 questions	27.0
Subset completing OSDI (n = 689)	
OSDI sum score ≥ 15 or more	31.5
OSDI sum score ≥ 15 or more and any of above 3 questions	13.7
OSDI sum score ≥ 15 or more but not any of above 3 questions	17.8
OSDI sum score < 15 or more and any of the above 3 questions	14.1

* Note: All 1635 participants were asked the following 3 questions as a proxy for having DED, which have been used separately in other population-based epidemiologic studies: (I) "Have you ever been diagnosed (by a clinician) as having dry eye syndrome?" (2) "Do you currently use artificial tear eye drops or gel?" and (3) "For the past three months or longer, have you had dry eyes? (This is described as a foreign body sensation with itching and burning, sandy feeling, not related to allergy)." If a participant answered yes to any of these questions, she was assigned as having DED.

In addition, a consecutive subset of 689 participants (from 394 families) attending for quantitative sensory testing completed the Ocular Surface Disease Index (OSDI) with an OSDI score of ≥ 15 used to define those with DED

Source: Vehof et al 2013[13]

Due to the paucity of formal prevalence and incidence estimates for DED and severe keratitis, the company used data reported by four sources to generate estimates of the incidence and prevalence of DED in England and Wales:

- A survey of 39,876 US women participating in the Women's Health Study[17]
- A survey among 25,444 US male physicians participating in the Physicians' Health Studies I and II[18]
- A systematic literature review of published epidemiological and healthcare resource use data supplemented with information obtained from interviewing 23 ophthalmologists in six European countries.[19] The company stated that this approach was used to model prevalence in the population under the age of 50
- Santen GmbH data on file[20] to estimate the prevalence of severe DED (derived from research assessing ophthalmologists' perceptions)

The company used the first three sources because they allow differentiation by specific age and by sex; as noted by the company (see Box 1), age and female sex are considered to be the most relevant systemic risk factors for DED. The overall prevalence of DED was estimated by the company to be 2.28%, of which 6% is estimated to be severe. It is not clear to the ERG how the final estimate was derived from the source papers. The first two published source papers suggest the prevalence of DED in those aged over 50 is around 7% in women[17] and 4% in men.[18] The ERG could not locate any specific estimates by age/sex group in the study by Clegg et al,[19] rather only estimated percentages of patients with DED in four age groups: <17 years (2% in UK), 17 to 45 years (18% in UK), 46 to 65 years (61% in UK) and over 65 years of age (19% in UK). The data on file provided by the company appear to suggest that the prevalence of DED of any severity in France is 6%, of whom, 12% have severe symptoms.20

Absent from the CS is any reference to the two different types of DED, namely:

- Evaporative DED caused by accelerated tear evaporation due to poor tear quality
- Aqueous tear-deficient DED caused by inadequate tear volume

Evaporative DED and aqueous tear-deficient DED may cause DED independently or they may present together. Evaporative DED is more common than aqueous tear-deficient DED. A retrospective observational cohort study[21] of patients with DED in the European Union and the United States found 49.7% had evaporative DED only, 14.5% had aqueous tear-deficient DED only and 35.8% had a mixture of the two types of DED. Aqueous tear-deficient DED is commonly part of, or secondary to, Sjögren's syndrome. Patients with Sjögren's syndrome are a subgroup identified by the NICE scope[22] (see section 3.6). Sjögren's syndrome is an

autoimmune condition which can affect many organ systems including a severe form of dry eye.[3] It has been reported that around 10% of patients with clinically significant aqueous tear-deficient dry eye have an underlying primary Sjögren's syndrome.[23] The prevalence of Sjögren's syndrome in severe DED is likely to be higher than 10%.

2.2 Critique of company's overview of current service provision

Section 2 of the CS provides information on current service provision which is summarised in Box 2. The ERG notes that no mention is made by the company in its description of service provision to autologous serum tears which may be offered to patients with very severe DED following the failure of treatment with CsA. The ERG further notes that artificial tear eye drops may be administered at the same time as CsA.

Box 2 Current service provision for patients with DED

- The majority of care provided to moderate to severe cases is managed by ophthalmologists; with updates transmitted periodically to the referring GP (Clinical Expert Interview with Professor Lightman, 2014)
- For patients with severe keratitis, treatment is mandatory to avoid the long term consequences of inflammation including ulceration and perforation which may lead to visual impairment and damage to corneal nerves through disease progression,[24] Treatment may also avoid the negative impact on functional visual acuity, resulting in impaired vision, ocular fatigue, inability to read or drive [25,26]
- Artificial tear products aim to alleviate symptoms by replacing or retaining moisture on the ocular surface and are recommended for patients with mild to moderate DED[7]
- Patients with mild to moderate symptoms may also be treated symptomatically with lubricants for long periods of time
- Other therapeutic strategies, such as ocular inserts, occlusion of the lacrimal puncta [punctal plugs], or anti-inflammatory treatment are available [27]
- Although topical steroids have shown some promise for improving the signs and symptoms of dry eye, their potential benefit in this chronic disease is limited by their known iatrogenic ocular side effects, e.g., intraocular hypertension, ocular infections, glaucoma and cataract[11,28-31] … In addition, all patients taking topical corticosteroids in the long-term require regular monitoring of IOP [intra-ocular pressure] and cataract formation [23]
- Ciclosporin [CsA] belongs to the family of medicines called immunosuppressants
- CsA has an anti-inflammatory effect on the cornea and the lacrimal (tear) gland [15] thereby reducing inflammation in the eye. This is important because dry eye is an inflammatory ocular disease evidenced by the inflammatory changes that occur on the entire ocular surface (the adnexa, conjunctiva and cornea)[3,10,11]
- It also increases tear secretion from the lacrimal gland by releasing neurotransmitters from sensory nerve endings, which interact with the parasympathetic nerves[32]
- More specifically, CsA inhibits the production and/or release of pro-inflammatory cytokines, and up-regulates the release of anti-inflammatory cytokines
- CsA pharmacy-compounded formulations are diverse with 0.05% to 2% ophthalmic emulsions in olive or castor oil administered up to four times daily
- However, in spite of its wide use, pharmacy-compounded CsA is not yet registered in Europe for this indication, is poorly controlled in terms of manufacturing quality and formulation, and while efficacy has not been clearly demonstrated, its safety profile appears acceptable
- Restasis, a 0.05% CsA ophthalmic emulsion, failed to obtain regulatory approved in Europe but succeeded to obtain FDA approval in the US in 2003
- A recent qualitative observational study[33] … observed that Restasis is used in more than 13 of the EU Member States

Source: Section 2 of the CS

As noted by the company, different formulations of CsA are currently used (off-label) in clinical practice. In the UK, these include CsA 0.05% (Restasis), CsA 2% eye drops and CsA 0.2% ointment (Optimmune). Restasis is licensed in the US by the FDA[34] for the treatment of DED but, as highlighted in Box 2, has no marketing authorisation for use in Europe. In the US, the severity of DED is not specified but guidelines by the American Academy of Ophthalmology recommend it for use for the treatment of moderate and severe DED.[23]

Ciclosporin, marketed as Ikervis by Santen GmbH, is not currently licensed for use in Europe but received a positive opinion[35] from the EMA CHMP on 22 January 2015. It is anticipated that Ikervis will be available in the UK in July/August 2015 for the treatment of severe DED.

Ikervis is a sterile, cationic (positively charged), oil-in water, unpreserved ophthalmic emulsion that contains CsA at a concentration of 1 mg/ml (0.1%). It is administered once a day at night time. The topical delivery of Ikervis is optimised by excipients such CKC that act as a cationic agent rather than as a preservative agent. The ERG notes that Restasis is an anionic (negatively-charged) oil-in-water emulsion typically administered twice daily.

In terms of numbers of patients likely to require Ikervis, as noted in section 2.1, the company estimates 2.28% of the England and Wales population aged between 19 and 90 have DED and, of these, 6% are likely to have severe DED, i.e. 61,302 people. The ERG considers the number of patients with severe DED is likely to exceed this figure because, based on the same source papers used by the company,[17-20] the proportions of patients estimated to have DED appear to be underestimates. However, as highlighted in section 2.1, obtaining an accurate and reliable estimate for DED prevalence is difficult and all currently available estimates should be used with caution.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2 displays the decision problem presented in the CS and that addressed by the company (CS Section 5). Each parameter is discussed in in the text following the table.

Table 2 NICE scope and company's decision problem

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

CFS=Corneal staining; DED=dry eye disease; DEWS=Dry Eye Workshop; HLA-DR=Human leukocyte antigens DR; OSDI=Oxford Surface Disease Index; TBUT=Tear film break up time; VAS=visual analogue scale

* The ERG notes that the exact intervention was the formulation of ciclosporin known as Ikervis as opposed to any ciclosporin formulation

† Trial evidence is actually only presented from Ikervis vehicle which contain different excipients in each trial whereas cost-effectiveness evidence assumes vehicle to be the same as AT

Source: Adapted from section 5 of the CS

3.1 Population

The population specified in the NICE scope is people with severe DED (DEWS [Dry Eye Workshop] 3 or 4) whose disease has not adequately responded to tear substitutes. The criteria used to define severe DED in the NICE scope (DEWS) represent one set of criteria for measuring severe DED; the ERG is aware that criteria may vary between geographical areas and healthcare professionals in clinical practice. The population defined by the company is patients with DED and severe keratitis which has not improved despite treatment with tear substitutes. Importantly, the population specified in the decision problem is identical to that of the proposed marketing indication for Ikervis. The ERG notes that patients with severe keratitis will also have severe DED as severe DED leads to severe keratitis.

Severe DED is defined differently in the two trials that provide supporting evidence of clinical effectiveness in the CS. In the pivotal SANSIKA trial,[36] it is defined using CFS (= 4), Schirmer's test without anaesthesia (≥ 2 mm/5 min and <10 mm/5 min) and OSDI (≥ 23). In the post-hoc analyses in the supportive SICCANOVE trial,[37] it is defined either as CFS = 4 or CFS ≥ 3 and OSDI ≥ 23. For pooling of efficacy data across both trials, it is defined as CFS = 4 and OSDI ≥ 23.

3.2 Intervention

The intervention specified by the scope and in the decision problem section of the CS is "Ciclosporin which provides immunosuppressive and anti-inflammatory effects for a disease that is considered to have an inflammatory component". However, as described in section 2.2 of the ERG report, different formulations of CsA exist and are currently being used off-label. The intervention addressed by the company in this appraisal is a formulation of CsA 0.1% once daily with the brand name Ikervis (see section 10.2.6, page 235 of the CS). This formulation is not currently used in NHS clinical practice. For the purpose of this appraisal, the company has considered this to differ from other formulations of CsA.

Ikervis is the intervention in the pivotal SANSIKA trial. The ERG notes that the Ikervis vehicle contains the CKC excipient whilst the CsA formulation used in the supportive SICCANOVE trial contains BAK instead of CKC. The reasons for the differences were queried by the ERG during the clarification process. The company confirmed that, during initial development, BAK was selected because of its extensive use in approved ophthalmic formulations. Subsequently, BAK was replaced by CKC since this is the most lipophilic of the three homologues in BAK. The selection of CKC instead of BAK resulted in a reduction of the amount of quaternary ammonium used by a factor of four. The company also confirmed, during the clarification process, that despite these differences in the vehicle, the CsA

formulations in each trial are considered to be similar and stated that this view was supported by the EMA CHMP. The ERG, however, notes the different AE profiles (rates of eye irritation, eye pain, site irritation and site pain and differences in rates of AE severity) of the intervention arm in the SANSIKA and SICCONOVE trials and suggests that this may be due to differences in the vehicle formulation.

3.3 Comparators

On page 34 of the CS, the company states "The decision problem addressed in the submission does not vary substantially from the scope." In fact, an examination of the company's decision problem table shows the wording used by the company to be identical to that used in the NICE scope.

However, adopting a different stance from the scope, the company does not believe AT or eye ointments are valid active comparators, a view the company states is shared by the EMA CHMP. Hence, the Ikervis vehicle, a sterile, drug-free, cationic ophthalmic emulsion containing no CsA (but containing CKC in SANSIKA and containing BAK in SICCANOVE) was used as the comparator in the presented clinical trial evidence. It should be noted, that the company does not consider the Ikervis vehicle to be a placebo "since eye drop vehicles are known to have some beneficial effect on their own" (CS, pages 7, 28 and 35). Importantly, it should also be noted neither vehicle used in the trials of Ikervis is a treatment commercially available anywhere in clinical practice (although it is noted that the company has previously stated the vehicle is similar to Cationorm ocular lubricant[22] which is used in some jurisdictions). Trial evidence provided by the company allowed patients in both the Ikervis and vehicle arms to receive AT. The comparator in the economic analysis conducted by the company is considered to be AT.

The ERG considers that other formulations of CsA which are currently used in clinical practice in England are the most appropriate comparators. For example, the company does not consider Restasis to be a valid comparator as it is not licensed in Europe and "does not target severe keratitis" (page 28 of the CS). The ERG disputes this statement for two reasons. First, the ERG is unaware of any specific evidence that shows whether Restasis targets severe keratitis or not. The ERG does, however, recognise that in the US, the severity of disease for which it is indicated is not specified (and the American Academy of Ophthalmology recommends its use for moderate to severe DED[23]). Second, while not licensed for use in Europe, the fact that it is currently used in clinical practice in England means it can be considered as a relevant comparator. The ERG also considers that other formulations of CsA (such as 2% CsA eye drops and Optimmune ointment) should be

considered comparators as they too are currently used in NHS practice. The ERG notes that a systematic review conducted on behalf of the company,[38] includes other formulations of CsA as comparators (see page 235 of CS).

3.4 Outcomes

The outcomes specified in the NICE scope largely related to the patient's experience of DED and its treatment, namely pain and discomfort, specific symptoms, AEs and HRQoL. Similar outcomes are addressed in the company's decision problem, although none of the specific symptoms in the NICE scope (photosensitivity, ability to open eyes, visual acuity, ability to concentrate) have been explicitly addressed. In addition, the company also considers objective signs of DED, including inflammation, corneal staining and tear osmolarity, and symptoms of ocular surface disease. The CS states that regulatory guidance recommends studying both signs and symptoms of the disease. The ERG notes that the company emphasises the lack of correlation between signs and symptoms (see section 2.1) and agrees that measuring the impact of treatment on signs is as important as measuring impact on symptoms (as well as AEs and HRQoL). This is because, as stated in the CS (page 35): "…severe inflammation is the main concern for ophthalmologists since it can lead to corneal ulceration and impaired vision. Therefore, treating severe inflammation and maintaining and protecting the integrity of the ocular surface is an important clinical challenge and deserves to be duly taken into consideration when designing a clinical study in DED patients." The use of co-primary endpoints and/or composite outcomes can therefore be justified. However, the ERG notes that the composite outcome used in the pivotal SANSIKA trial has not been validated and the clinical significance of changes in the outcome are unclear (although considered separately, the CFS and OSDI endpoints are meaningful).

In addition, the ERG notes that the list of outcomes included in the stated decision problem is not an exhaustive list; additional outcomes were assessed in the CS. These outcomes include changes in lissamine green staining, change in Schirmer's tear test, use of AT and investigator global evaluation of efficacy (see section 4.2.2).

3.5 Economic analysis

The company's results are expressed in terms of incremental cost per QALY gained as specified in the NICE scope. The NICE scope also specifies that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The timespan considered in the company's economic analysis is a life-time horizon, which is appropriate. Costs are considered from the perspective of the NHS.

In its economic analysis, the company compared Ikervis plus AT with AT; in this comparison the Ikervis vehicle is considered to be a proxy for AT. The ERG considers other formulations of CsA to be appropriate comparators. In the absence of any robust clinical evidence comparing Ikervis to another CsA formulation, the ERG considers that it is appropriate to carry out a cost minimisation analysis assuming all CsA based treatments are of equivalent efficacy, are associated with similar AEs and incur similar administration, prescribing and monitoring costs. When this approach is adopted, the comparison reduces to selecting the option available to the NHS with the lowest acquisition cost.

3.6 Subgroups

The NICE scope states that patients with Sjögren's syndrome should be considered. The company states 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. The reasoning provided by the company was that because only 92 patients in the pivotal SANSIKA trial had Sjögren's syndrome it was not considered feasible to conduct a cost effectiveness analysis. The ERG agrees with the company's view.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The search strategies used to identify papers for the company's systematic review are described in section 6.1 and Appendix 2 of the CS. These searches were conducted in MEDLINE, MEDLINE In-process, Embase (all OVID SP) and CENTRAL (via the Cochrane library). They were carried out on 21 July 2014 and the databases were searched from inception to that date. PubMed was also searched, but limited to e-publications ahead of print. No grey literature websites were searched but the company did search for relevant conference proceedings. Overall, the ERG considers the search strategies to be sufficiently comprehensive and the search terms to be relevant for this drug and condition. However, limiting the searches of the Cochrane library databases to CENTRAL was unusual and risked missing relevant studies via other sources, such as any studies included in systematic reviews identified via the Cochrane Database of Systematic Reviews.

To ascertain whether the company had missed any relevant studies the ERG conducted its own searches (summarised in Appendix 1, section 10.1, of this report). The ERG's search, conducted on 22 December 2014, identified two recently published systematic reviews[39,40] of CsA for the treatment DED (of any severity). Included in these systematic reviews were additional RCTs not included by the company. The relevance of these RCTs to the scope and decision problem is explored further in section 4.2.1.

4.1.2 Eligibility criteria

The eligibility criteria for the systematic review are reported in Appendix 2 of the CS (section 10.2.7, page 236) and reproduced in Table 3. The population is compatible with that outlined in the company's decision problem. However, the ERG notes that the intervention is Ikervis, which is more specific than 'ciclosporin', the intervention specified in both the NICE scope and the company's decision problem. Additional comparators and outcomes were also included. For the systematic review, these include other formulations of CsA which the ERG considers are the most relevant comparators to Ikervis. Other comparators, including punctal plugs, permanent punctal occlusion and autologous serum, are considered by the ERG to be of less relevance to the NICE scope or company's decision problem. This is because these are likely to be treatment options after failure of CsA rather than as alternatives to CsA. Indeed, in the company's economic model, punctal plugs are a treatment option for patients following treatment with Ikervis (see section 5.4.3). In terms of outcomes, while the ERG considers the additional outcomes to be relevant to the NICE scope and company's decision

problem, including or excluding studies based on outcomes is not recommended as it may introduce reporting bias.[41]

Table 3 Eligibility criteria used for the company's systematic review

Patients	Adult patients (≥ 18 yr) with severe keratitis with dry eye disease (DED) which has not improved despite treatment with tear substitutes Severe DED was defined as follows: • DEWS 3 or 4 or two of the following criteria being met: 1. Schirmer's test score (with or without anaesthesia) ≤5 mm/ 5min 2. Tear-film break-up time (TBUT) score ≤5 seconds 3. OSDI ≥ 23 (0 to-100 scale)
Intervention	Ciclosporin-A (Ikervis)
Comparators	• Ciclosporin-A (CsA) • Punctal plugs • Permanent punctal occlusion • Autologous serum • Artificial tears • Cholinergic agonists • Acetylcysteine drops • Topical Corticosteroids
Outcomes	Efficacy outcomes • Corneal fluorescein staining (CFS) score assessed with the Oxford[42]/modified Oxford scale [43], NEI/IW scale, van Bijsterveld scale, Shimmura scale, ORA scale or other independent scales • Ocular surface disease index (OSDI) score • Visual analogue scale (VAS) score • Schirmer-I test score (without anaesthesia) • Tear film break up time (TBUT) • Complete corneal clearing • Artificial tear use • Investigator global evaluation of efficacy Safety outcomes • Grade 3/4 adverse events (AE) only • Overall incidence of adverse events • Withdrawal due to adverse events • Serious adverse events (SAE) • Individual adverse events: blepharitis, eye irritation, instillation site pain, eye pain, conjunctival hyperaemia and nasopharyngitis
Study design	Randomised controlled trials (RCTs)

Source: page 236 of the CS

The CS notes that during the screening of full publications, review discrepancies in the reporting of patient severity were noted. To ensure consistency across the studies, the DEWS 2007 dry eye severity grading scheme[3] was used. Where studies pre-dated the publication of DEWS 2007 or alternative diagnostic measures were used, severity was determined based on Schirmer's test score, TBUT and/or OSDI (from the study's eligibility criteria or baseline characteristics). If disease severity was unclear, studies were appropriately excluded.

However, page 43 of the CS notes that these criteria were not always strictly adhered to. Three studies were in fact included for other reasons where a severe DED population was indicated based on TBUT and baseline values[44] or Schirmer's test score and CFS;[45,46] one of these studies[45] also stated "56 patients with severe keratoconjunctivitis sicca were enrolled".

4.1.3 Data abstraction strategy

Data were appropriately extracted by a single reviewer and cross-checked by a second reviewer.

4.1.4 Quality assessment

The completed tool used for quality assessment is presented in section 6.4.1 (page 95) of the CS (Table B9). Quality assessment included elements of the tool for assessing risk of bias recommended by the Cochrane Collaboration.[47] The ERG agrees this is an appropriate tool for assessing the quality of RCTs.

4.1.5 Evidence synthesis

The trials included in the company's systematic review had heterogeneous populations. Hence, the majority of the evidence was, therefore, appropriately presented narratively. Data for CFS-OSDI response reported for patients with Sjögren's syndrome and for treatment-emergent AEs for all patients were, however, pooled. In both instances this appears to have been carried out to improve precision of estimates.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Identified studies

The company's search yielded 1726 citations, of which, 31 studies were included in its systematic review. However, in the CS the company only presents evidence for two phase III trials (SANSIKA and SICCANOVE), both of which compared Ikervis to a vehicle and both of which were sponsored by the company. A third trial of Ikervis, a phase IIb trial (ORA)[48] was excluded by the company. During the clarification process the company explained that ORA[48] had been excluded because patients in that trial had mild to moderate DED and, therefore, the company did not consider the study to be pivotal or results supportive to the research question. The ERG agrees with this reasoning.

Page 50 of the CS states: "The patient population recruited into the SANSIKA trial appeared to be the only trial which clearly defined patients with severe keratitis and severe DED." The ERG interprets this as meaning this was the only trial relevant to the population specified in the company's decision problem. However, the company also presented evidence from the SICCANOVE trial which included patients with moderate to severe DED patients. The ERG notes that post-hoc analyses of patients with severe DED were conducted in this trial and the ERG considers that only these post-hoc analyses are relevant to the decision problem.

Data from the 31 studies included in the systematic review were presented and synthesised in a standalone systematic review report that was commissioned by the company[38] which was made available at the ERG's request. The ERG notes that, in addition to the three aforementioned Ikervis trials, the review included five Restasis RCTs.[44,46,49-51] The results of these trials may be of relevance to the decision problem since Restasis is a CsA formulation. However, the company considers that Ikervis and Restasis are not equivalent, that the vehicles are not equivalent and concludes that data from Ikervis and Restasis trials should not be pooled in a meta-analysis. The ERG agrees with the company that the vehicles used as comparators in Ikervis and Restasis trials are not homogeneous, thus precluding a meta-analysis.

Unlike the company, but in agreement with the authors of the systematic review report, the ERG considers Restasis to be an appropriate comparator. However, no formal indirect treatment comparison could be conducted between Ikervis and Restasis because there is no common comparator treatment to link the trials.

The only meta-analysis presented in the CS were data pooled from the SANSIKA and SICCANOVE trials for the subgroup of patients with Sjögren's syndrome (including only

severe DED patients from SICCANOVE). This was only conducted for CFS-OSDI response at month 6. Additional data were also pooled by the company in analyses provided during the clarification response. The ERG considers these to be of less relevance to the decision problem than the subgroup meta-analysis presented in the CS.

Studies identified by the ERG's search

The ERG's own searches identified two published systematic reviews of CsA for DED (of any severity).[39,40] These included a total of 20 RCTs,[46,50-68] three of which[46,50,51] were included in the standalone systematic review.[38] However, none of the RCTs identified from the ERG's searches included Ikervis as an intervention or comparator and so are not directly relevant to this appraisal.

In addition to the two completed systematic reviews,[39,40] the ERG's searches also identified a protocol for a Cochrane Review which is currently in progress.[69] During the clarification process the company confirmed that it had not contacted the authors of this review. Contacting the authors of ongoing reviews is often a good method for ensuring all relevant trials are identified. However, given the company is the sponsor of Ikervis, the ERG is confident that all relevant Ikervis trials have been identified in this instance.

4.2.2 Trial characteristics

SANSIKA and SICCANOVE were phase III trials conducted in Europe. Patients were randomised using ratios of Ikervis to vehicle of 2:1 and 1:1 in the SANSIKA trial and the SICCANOVE trial respectively. The interactive voice response system (IVRS) was used to assign patients to treatment groups in both trials, ensuring that allocation concealment was achieved. Randomisation was stratified according to centre in SANSIKA and presence/absence of Sjögren's syndrome in SICCANOVE. The ERG is satisfied that randomisation was carried out appropriately and allocations were adequately concealed in both trials.

In both trials, treatment was received for 6 months. In the SANSIKA trial, patients could be treated for an additional 6 months with Ikervis, meaning that some patients received Ikervis for 12 months in total. Other patients crossed over from vehicle and received Ikervis during the last 6 months of the study. The first 6 months of the trial is known as SANSIKA part 1 and the second 6 months as SANSIKA part 2; the primary aim of part 2 was to derive longer term safety data.

The key trial characteristics are summarised in Table 4.

Table 4 Summary of trial characteristics of SANSIKA and SICCANOVE

Characteristic	SANSIKA	SICCANOVE
Location	France, Germany, Italy, Czech Republic, Spain, UK, Belgium, Sweden, Austria	France, Germany, Italy, Czech Republic, Spain, UK
Design	Multicentre, randomised, double-blind, 2 parallel arm, vehicle-controlled, 6-month phase III trial (part 1) plus a 6 month open label treatment safety follow-up period (part 2)	Multicentre, randomised, double-blind, 2 parallel arm, vehicle-controlled, 6-month phase III trial
Population	Severe DED defined using CFS (= 4), Schirmer's test without anaesthesia (≥ 2 mm/5 min and <10 mm/5 min) and OSDI (≥ 23)	Moderate to severe DED defined using a scale measuring ocular discomfort, TBUT, CFS, Schirmer's test without anaesthesia and lissamine green staining; post-hoc analyses for severe DED were based on CFS (= 4) or CFS (≥ 3) and OSDI (≥ 23)
Intervention	Ikervis 0.1%	Ikervis 0.1%
Comparator	Vehicle (containing CKC)	Vehicle (containing BAK)
Primary outcomes	Composite endpoint, % responders based on CFS-OSDI composite endpoint: • Improvement of ≥ 2 points from baseline in corneal fluorescein staining (CFS) based on the modified Oxford scale • Improvement by ≥ 30% from baseline in Ocular Surface Disease Index (OSDI)	Co-primary endpoints: • Change in CFS (Modified Oxford Scale) • Change in global score of ocular discomfort (VAS)
Pre-specified secondary outcomes	Signs: • Change in CFS score • Complete Corneal Clearing • % responders based on CFS • Change in Schirmer's test score without anaesthesia • Change in lissamine green staining score • Change in tear break up time (TBUT) • Impression cytology for conjunctival cell surface human leukocyte antigen-DR (HLA-DR) expression • Tear film osmolarity. Symptoms: • Change in OSDI score • % responders based on OSDI • Change in global ocular discomfort (VAS) • % of responders based on improvement in ocular symptoms (VAS) Other: • Artificial tear use • Investigator global evaluation of efficacy • Health-related Quality of Life (NEI-VFQ and EQ-5D) • Safety	Signs: • Change in CFS score • Complete Corneal Clearing • % responders based on CFS • Change in Schirmer's test score without anaesthesia • Change in lissamine green staining score • Schirmer's test score without anaesthesia • Change in TBUT Symptoms: • Change in OSDI score • Change in global ocular discomfort (VAS) • Change in VAS score for each symptom • % of responders based on improvement in ocular symptoms (VAS) Other: • Artificial tear use • Investigator global evaluation of efficacy • Safety

BAK-Benzalkonium chloride; CKC=Cetalkonium chloride; EQ-5D=European Quality of Life-5 Dimensions; NEI-VFQ=National Eye Institute Visual Function Questionnaire; VAS=Visual analogue scale

Source: Adapted from Table B3 of the CS

The ERG notes the following important differences between SANSIKA and SICCANOVE:

- SANSIKA only included patients with severe DED whereas SICCANOVE included patients with moderate to severe DED; only patients with severe DED are relevant to the decision problem (SICCANOVE did conduct post-hoc analyses for patients with severe DED)
- In SANSIKA an excipient used in the vehicle was CKC whereas in SICCANOVE it was BAK; the Ikervis formulation used in SANSIKA is the formulation that the company has applied for a marketing authorisation for and thus is being proposed for use in clinical practice
- There was no restriction in concomitant AT use in either the Ikervis or vehicle arm in SANSIKA whereas in SICCANOVE it was capped at a dose of 6 drops a day; in clinical practice, it is unlikely that AT use would be capped

The primary endpoint for the SANSIKA trial was the composite CFS-OSDI response (defined as improvement of ≥ 2 points in CFS and an improvement by ≥ 30% in OSDI) which measures signs and symptoms. While both CFS and OSDI are recognised and validated instruments for measuring signs and symptoms respectively, the validity of using CFS-OSDI as a composite outcome is not known. In particular, it must be considered whether the concept of a CFS-OSDI responder is a valid one in clinical practice and if so, what the thresholds should be to define a responder. In the treatment of severe DED in clinical practice, signs of corneal dryness and keratitis (measured by CFS) are paramount in defining an improvement with treatment. In clinical studies, a range of both signs and symptoms may be formally assessed but rarely are participants classified as responders, either for individual endpoints or for a composite outcome. The ERG notes that none of the studies of CsA included in previous systematic reviews[39,40] defined patients as responders based on CFS-OSDI. If the concept of a CFS-OSDI responder is accepted as a valid one, there also remains doubt about what the thresholds for CFS and OSDI improvements should be. To a large extent, this must also depend on the criteria used for determining severe DED. If, as in SANSIKA (and some post-hoc analyses in SICCANOVE), patients must have CFS = 4 at baseline, a CFS improvement of ≥ 3 or = 4 may arguably be preferred to an improvement in CFS of ≥ 2. Similarly, the validity of an OSDI improvement of 30% may be questioned as this may be considered to be either too stringent or not stringent enough.

Given both signs and symptoms are important outcomes, there is also merit in attempting to capture efficacy this way. However, to date, it has not been used as a validated and universally accepted outcome.

4.2.3 Participant characteristics

In total, 261 patients were randomised in the SANSIKA trial. Figure B3 (page 94 of the CS) shows that data from 15 patients were not considered to be valid. It is stated in the draft EPAR[35] that these patients were all from one study centre where breaches of good clinical practice led to concerns about reliability of the data. Hence 246 patients were included in SANSIKA with baseline data available for 245 patients, 154 in the Ikervis arm and 91 in the vehicle arm. Of these, 208 patients completed part 1 (Ikervis: 129; vehicle: 79) and 177 completed part 2 (114 who remained on Ikervis for 12 months and 63 who switched from vehicle to Ikervis after 6 months). While 496 patients were enrolled in the SICCANOVE trial and baseline data were available for 489 patients, not all these patients had severe DED. The company defined severe DED in two ways: CFS ≥ 3 and OSDI ≥ 23 or CFS = 4. Using the former definition, 246 (50%) of patients had severe DED and using the latter, 85 (17%).

The participant characteristics of the SANSIKA and SICCANOVE trials are provided in Table B5 (of the CS, page 65). Baseline characteristics are not provided for patients with severe DED in the SICCANOVE trial. The company states that demographic and baseline disease characteristics of participants were well balanced between treatment groups in both trials. Some differences for the following baseline characteristics reported in the CS were observed by the ERG:

- Proportionately more males in the Ikervis arm (18.2%) than the vehicle arm (8.8%) in SANSIKA
- Mean ± SD time since diagnosis in both the SANSIKA (Ikervis: 8.8 ± 7.1 years; vehicle: 9.7 ± 6.7 years) and SICCANOVE trials (Ikervis: 7.2 ± 6.8 years; vehicle: 8.0 ± 8.4 years); the median time also differed in the SANSIKA trial (Ikervis: 6.2 years [range: 0.2 to 31.5]; vehicle: 8.7 years [range 0.2 to 30.7) but not in the SICCANOVE trial (Ikervis: 5.1 years [range 0.1 to 38.3]; vehicle: 5.2 years [range 0 to 64.1]).
- Median OSDI score at baseline in SANSIKA was 62.50 (range 25 to 100) in the Ikervis arm and 58.33 (range 25 to 100) in the vehicle arm; in SICCANOVE it was 45.23 (range 0 to 100) and 39.58 (range 0 to 100) in the Ikervis and vehicle arms respectively.

However, the ERG does not consider that any of the differences in baseline characteristics between arms would likely bias the intervention over vehicle or vice versa although it is noted that males tend to have less severe DED than females and so the difference in sex may introduce some bias in favour of Ikervis. On the other hand, an observed difference in immune system disorders reported in the CSR (11.7% in Ikervis and 5.5% in vehicle) may have introduced some bias in favour of vehicle. Similarly, a greater proportion of surgical and medical procedures (12.3%) in the Ikervis arm than vehicle (3.3%) may also have introduced some bias in favour of vehicle assuming the surgical procedures to be related to the eye.

Generally, based on baseline characteristics, the ERG concludes that patients in the SANSIKA trial (and patients included in post-hoc analyses in SICCANOVE) are a similar patient population to that specified in the final scope issued by NICE and in the company's decision problem. Based on participant characteritics reported, the ERG also believes the results from the SANSIKA patient population are likely to be generalisable to the patient population that would be treated in the UK.

4.2.4 Description and critique of the statistical approach

Details of the sample size calculations performed for SANSIKA and SICCANOVE are reported in the study protocols. The ERG is satisfied with the pre-specified sample size calculations reported.

The ERG notes that the SANSIKA CSR states that there were no protocol amendments. There were several changes to the statistical analyses which are documented in Table 3, page 75 of the CSR. The ERG is satisfied that these amendments took place before database lock and so were not driven by the results and are not therefore likely to be a source of bias.

In both the SANSIKA and SICCANOVE trials the full analysis set (FAS), which included all randomised patients who received any amount of the study drug, was used for the efficacy analyses; according to the treatment group to which patients were originally randomised. The safety analysis set (SAF) considered all randomised patients for whom there was any evidence that study medication had been used. In the SANSIKA trial there were 245 (99.6%) patients in the FAS (Ikervis: 154; vehicle: 91) and 244 (99.2%) in SAF (Ikervis: 154; vehicle: 90). In the SICCANOVE trial there were 489 (99.8%) patients in the FAS (Ikervis: 241; vehicle: 248) and 492 (99.2%) in the SAF (Ikervis: 242; vehicle: 250) but only a (non-randomised) sample of these patients (those with severe DED) are relevant to the decision problem. As argued by the company (page 80 of the CS): "The FAS is as complete as possible and as close as possible to the ITT [intention-to-treat] ideal of including all randomised patients. It is also considered in many circumstances to provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice."

For all efficacy data, the last observation carried forward method was used to impute missing values. Supportive analyses for the primary outcomes for both studies were performed to provide evidence of robustness of these results. These included an assessment of the FAS observed data (according to the randomised treatment group), per protocol population and other methods of imputation of missing cases and alternative methods of analysis. The ERG is satisfied that appropriate methods have been used.

In addition to analyses of pre-specified secondary outcomes, a number of post-hoc subgroup analyses were conducted, particularly in subsets of patients with severe DED (defined as CFS ≥ 3 and OSDI ≥ 23 or CFS = 4 respectively) in SICCANOVE (see Table 5). These included defining a more stringent composite outcome (CFS ≥ 3 and OSDI ≥ 30%) as a post-hoc secondary analysis and this is the outcome utilised in the cost effectiveness analysis (see section 5.4.7). A large number of post-hoc analyses would normally be considered a potential issue for concern; in SICCANOVE the ERG notes that these were used to inform pre-specified analyses subsequently conducted in SANSIKA. The post-hoc analyses from this trial were therefore considered only exploratory and tested in SANSIKA and the ERG agrees this is an appropriate approach to adopt.

In SANSIKA, descriptive statistics of AEs were presented and post-hoc analyses, of all AEs that occurred after the first instillation of Ikervis or vehicle in the SAF patients who received during part 1, were performed at the end of part 2 to provide a safety overview of the active product over 12 months. Descriptive statistics were presented for AEs in SICCANOVE and an ANCOVA model was used to analyse the data at 6 months. The ERG considers these are appropriate methods for analysing AEs.

HRQoL was only measured in SANSIKA. Two measures were utilised: NEI-VFQ-25, an ophthalmic specific questionnaire, and EQ-5D, a generic health questionnaire. Both questionnaires are considered by the ERG to be appropriate for measuring HRQOL.

Table 5 Post-hoc analyses conducted in SANSIKA and severe DED populations in SICCANOVE

Outcome	SANSIKA	SICCANOVE
Signs and symptoms	• Primary outcome (CFS-OSDI response) at months 1 and 3 (CFS ≥ 2 and OSDI ≥ 30%) • CFS-OSDI response using more stringent criteria (CFS ≥ 3 and OSDI ≥ 30%)	• CFS-OSDI response rate (CFS ≥ 2 and OSDI ≥ 30%) in patients with both CFS ≥ 3 and OSDI ≥ 23 at baseline*
Signs	• CFS responder rate in patients with ≥ 3 improvement in CFS • Worst tear film osmolarity in patients with a score higher than 308 mOsms/L at baseline	• Change in CFS in patients with CFS = 4 at baseline • Change in lissamine green staining in patients in patients with CFS = 4 at baseline • Change in Schirmer's test score in patients in patients with CFS = 4 at baseline • CFS response in patients with CFS = 4 at baseline and patients with both CFS ≥ 3 and OSDI ≥ 23 at baseline • CFS response (≥ 2) patients with CFS = 4 at baseline and patients with both CFS ≥ 3 and OSDI ≥ 23 at baseline
Symptoms	None	• OSDI response rate (OSDI ≥ 30%) in patients with both CFS ≥ 3 and OSDI ≥ 23 at baseline*
Other	• Safety analyses of all ocular AEs that occurred after the first instillation of Ikervis during Part 1 were performed at the end of Part 2 to provide a safety overview of the active product over 12 months	None

* Additional post-hoc analyses using different criteria for measuring response by change in OSDI were also conducted and reported in the SICCANOVE CSR

Source: CS and SICCANOVE CSR

Pooled data from SANSIKA and SICCANOVE

Meta-analyses were presented in the CS for CFS-OSDI response at month 6 using imputed data in the Sjögren's syndrome set in from the FAS and in severe FAS (CFS = 4 and OSDI ≥ 23); the ERG notes that the definition of severe DED here differs slightly to that used for SICCANOVE alone (CFS ≥ 3 and OSDI ≥ 23 or CFS = 4). The ERG requested clarification on the methods used and whether the analysis was pre-specified. The company responded that the analysis was specified in 2012, a time when the results of the SICCANOVE trial were available but the SANSIKA trial was still blinded. The company stated that a fixed effects model had been used. The ERG also notes that descriptive post-hoc subgroup meta-analyses results for the change in CFS score in the FAS population according to age, gender, menopausal and Sjögren's status, age and duration of the disease are also reported

in the draft EPAR.[35] Additional meta-analyses were also provided during the clarification process. Only the meta-analyses presented in the CS for the subgroup of patients with severe DED and Sjögren's syndrome (severe FAS) are considered relevant to the decision problem by the ERG.

The ERG notes that in the company's presentation of the results, the forest plot lacks important detail commonly reported with the presentation of meta-analyses such as the weight given to each study and a test for heterogeneity (such as I^2). As such, the ERG has some concerns that the data may have been simply pooled by adding the data together rather than using standard techniques for conducting meta-analyses. This would also mean that the randomisation in the individual studies is unlikely to be preserved.

AE data were also pooled to assess safety. During the clarification process, the company confirmed that no specific meta-analysis model was used for the analysis and descriptive statistics were provided. However, the ERG also notes the data presented include an estimate for relative risk between treatment arms, implying statistical analyses were conducted that were not simply descriptive.

4.2.5 Risk of bias

As recommended by the Cochrane Collaboration,[47] the company conducted assessments of the risk of bias for the SANSIKA and SICCANOVE trials. These assessments are presented in Table B9 of the CS (page 95) and summarised in Table 6. The ERG concurs with the company's risk of bias conclusions and agrees that both the SANSIKA and SICCANOVE trials have a low risk of bias. It is noted that while an ITT analysis was not used in either trial, the FAS was used in both trials. As explained in section 4.2.4, the FAS was almost identical to the intention to treat ITT population which is considered the ideal for RCTs as it includes all randomised patients. However, as also noted in section 4.2.4, only a non-randomised sample of patients with severe DED in SICCANOVE are relevant to the decision problem.

Table 6 Quality assessment results for SANSIKA and SICCANOVE

Trial no. (acronym)	Phase III SICCANOVE (NVG06C103)	Phase III SANSIKA (NVG10E117)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No*	No*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No- full analysis set used which included all randomised patients who received any amount of the study drug, analysed according to their randomised group.	No- full analysis set used which included all randomised patients who received any amount of the study drug, analysed according to their randomised group.

* The ERG notes that not all post-hoc analyses were reported in the CS and detailed findings for the change in OSDI were not reported in the CS

Source: Table B9 of the CS

4.2.6 Results

While changes over time were reported for every efficacy outcome measured in both treatment arms in both trials, very few between arm differences were reported to be statistically significant at 6 months. Perhaps importantly, the primary outcome for SANSIKA showed no statistically significant difference between the Ikervis and vehicle arm and only one of the primary co-endpoints (change in signs measured by CFS score) was statistically significant between arms in SICCANOVE; mean ± standard deviation (SD) change in CFS was -1.05 ± 0.98 in the Ikervis arm versus -0.82 ± 0.94 in the vehicle arm ($p = 0.009$) and mean ± SD change in symptoms measured by VAS was -12.82 ± 18.59 versus -11.21 ± 19.35 respectively ($p = 0.808$). Since SICCANOVE included patients with moderate to severe DED, only post-hoc analyses conducted in patients with severe DED are referred to in the remainder of this report. Key findings for both trials are reported in Table 7.

An interesting finding is that the difference in CFS-OSDI response rate was much greater in the severe DED population in SICCANOVE (25.2%) compared to SANSIKA (5.4%); the difference is attributable to a much lower response rate in the vehicle arm of SICCANOVE (5.6%) than SANSIKA (23.1%). It is not clear why such a difference should be evident but the ERG speculates it may be as a result of different AT use in the trials; mean use of AT

appearing to be higher in both arms of SANSIKA than in either arm of SICCANOVE (where the use of AT was capped).

A summary of all the findings presented in the CS which were and were not statistically significant are presented in Table 8. The only statistically significant findings reported between arms at 6 months in SANSIKA were for the following measures of signs:

1. Changes in CFS (which was the only outcome analysed post-hoc in SICCANOVE that showed a statistically significant difference between arms in both trials)
2. CFS improvements ≥ 3 (post-hoc outcome)
3. CFS-OSDI responder rate using definition of CFS response ≥ 3 (post-hoc outcome)
4. Impression cytology: HLA-DR (AUF)
5. Worst tear-film osmolarity in patients with elevated tear film osmolarity at baseline (post-hoc outcome)

Non-statistically significant findings were reported for the following measures of signs in SANSIKA:

1. CFS improvement of ≥ 2 points
2. Complete corneal screening
3. Complete responders based on CFS
4. Change in Schirmer's Test score without anaesthesia
5. Change in lissamine green staining score
6. Change in TBUT
7. Impression cytology: HLA-DR + conjunctival cells, presenting an expression of the inflammatory marker HLA-DR (HLA-DR + cells)
8. Mean (SD) tear film osmolarity

There were no statistically significant differences between arms for measures of symptoms, use of AT or investigator global evaluation of efficacy in SANSIKA.

Table 7 Summary of Key findings from SANSIKA and SICCANOVE*

Outcome (primary outcomes in shaded cells)	SANSIKA		SICCANOVE	
	Ikervis	Vehicle	Ikervis	Vehicle
CFS-OSDI response – FAS Imputed data (according to the randomised treatment group) for SANSIKA and severe population for SICCANOVE				
N	154	91	43	42
Responders, n (%)	44 (28.6)	21 (23.1)	(30.8) †	(5.6) †
Non-responders, n (%)	110 (71.4)	70 (76.9)	(69.2) †	(94.4) †
CFS response (change in CFS ≥ 2)*				
N	154	91	Not applicable	Not applicable
Responders, n (%)	80 (51.9)	41 (45.1)	Not applicable	Not applicable
Non-responders, n (%)	74 (48.1)	50 (54.9)	Not applicable	Not applicable
OSDI response (change in OSDI ≥ 30%)*				
N	154	91	Not applicable	Not applicable
Responders, n (%)	61 (39.6)	36 (39.6)	Not applicable	Not applicable
Non-responders, n (%)	93 (60.4)	55 (60.4)	Not applicable	Not applicable
Change in CFS*				
N	132	83	43	42
Mean (± SD)	-1.81(± 1.27)	-1.48(± 1.08)	-1.47 (± 1.162)	-0.69 (± 1.047)
Median (Range)	-2 (-4 to 1)	-1 (-4 to 0)	-1 (-2 to -1)	-1 (-1 to 0)
Change in Global Score of Ocular Discomfort (VAS)*				
N	120	75	Not applicable for severe DED	Not applicable for severe DED
Mean (± SD)	12.97 (± 22.73)	-10.47 (± 21.55)	Not applicable for severe DED	Not applicable for severe DED
Median (Range)	-11.07 (-59.8;66.6)	-10.38 (-59.5;38.5)	Not applicable for severe DED	Not applicable for severe DED

* Change in CFS and OSDI could only be determined where baseline and end of study data were available in SANSIKA; only imputed data for CFS response and OSDI response were presented for SANSIKA

† Response rate data were only reported in relation to the calculation of the SANSIKA sample size in the CS (page 86) and confirmed by the company during the clarification response to be a post-hoc analysis in the severe DED population (CFS = 4 and OSDI ≥ 23); in the CSR the response rates differ, in the population with CFS ≥ 3 and OSDI ≥ 30 at baseline (n = 246) the response is 19.53% versus 10.17% (p = 0.049) and in population of patients with CFS = 4 at baseline is 32.56% versus 7.14% (p = 0.003) (n = 85)

Source: Adapted from Table B10 (of the CS with additional data from Tables 16 and 18 of SANSIKA CSR and Table 2.1.20 of SICCANOVE CSR; only between arm statistically significant difference is change in CFS in SANSIKA and SICCANOVE and CFS-OSDI response in SICCANOVE

Table 8 Summary of whether efficacy results presented in CS were statistically significant in SANSIKA and post-hoc analyses in SICCANOVE (severe DED)

Outcomes	Statistically significant?	
	SANSIKA	SICCANOVE
Signs & Symptoms (composite outcomes)		
% responders of CFS (≥ 2) and OSDI (≥ 30%)	✗ Primary	✓ * †
% responders of CFS (≥ 3) and OSDI (≥ 30%)	✓ post-hoc	N/A
Signs		
Change in CFS	✓	✓ †
CFS improvement of ≥ 2 points	✗	✓ * †
CFS improvement of ≥ 3 points	✓ post-hoc	N/A
Complete corneal screening	✗	N/A
% complete responders based on CFS	✗	N/A
Change in Schirmer's Test score without anaesthesia	✗	✓ †
Change in lissamine green staining score	✗	✓ †
Change in TBUT	✗	N/A
Impression cytology: HLA-DR (AUF)	✓	N/A
Impression cytology: HLA-DR expression (HLA-DR +)	✗	N/A
Mean (SD) tear film osmolarity	✗	N/A
Worst tear film osmolarity	✓ post-hoc ¥	N/A
Symptoms		
Change in global ocular discomfort (VAS)	✗	N/A
% of responders based on improvement in ocular symptoms (VAS) §	✗	N/A
Change in OSDI	✗	N/A
OSDI response: improvement of ≥ 30%	✗	✗ *
Other		
Median use of artificial tears	✗	N/A
Investigator global evaluation of efficacy	✗	N/A

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

* SICCANOVE post-hoc subgroup analysis in patients with severe DED defined as CFS ≥ 3 and OSDI ≥ 23 at baseline

† SICCANOVE post-hoc subgroup analysis in patients with severe DED defined as CFS = 4 at baseline

¥ SANSIKA post-hoc subgroup analysis in patients with elevated tear film osmolarity at baseline

§ ≥ 30% global ocular discomfort (SANSIKA) or ≥ 25% global ocular discomfort (SICCANOVE)

Source: Section 6.5 of CS and pages 10 to 11 of SICCANOVE CSR

The primary outcome in SANSIKA, CFS-OSDI response rate (with response defined as improvement of ≥ 2 points in CFS and an improvement by ≥ 30% in OSDI) was not statistically significant between arms at 6 months. Similarly there was no statistically significant difference in CFS response or OSDI response when measured individually although the responder rate tended to be higher for signs (CFS) compared to variables assessing symptoms of ocular discomfort (OSDI) (Table 7). The CFS and OSDI responder rates did however continue to increase over time. In SANSIKA part 2, CFS response was 51.9% at 6 months and 65.6% at 12 months and OSDI response was 39.6% and 52.3% respectively. The CFS responder rate at 12 months in those who crossed over from vehicle to Ikervis was 54.4% while the OSDI response rate for patients who crossed over (reported only in the CSR, Table 35) was 55.7%.

While CFS response was not statistically different between trial arms, the difference in change in CFS was statistically significant at 6 months (Table 7): adjusted mean change in CFS score from baseline was -1.76 with Ikervis and -1.42 with vehicle (p = 0.037). The change in OSDI (reported in the SANSIKA CSR as -13.6 with Ikervis and -14.1 with vehicle) on the other hand was not statistically significant.

A post-hoc analysis of change in CFS in which the response rate was more stringently defined (an improvement of ≥ 3 points in CFS) resulted in a statistically significant difference between treatment arms based on both imputed (p = 0.002) and observed (p = 0.001) data. The proportion of responders in the Ikervis arm was 31.2% (imputed data) or 35.6% (observed data) and 13.2% (imputed data) and 14.5% (observed data) in the vehicle arm. The difference between arms was thus much greater using CFS ≥ 3 (18% using imputed data) than when measuring response as a change in CFS ≥ 2 (6.8% from imputed data, observed data were not available).

This difference in CFS also translated into a statistically significant difference in CFS-OSDI response using the more stringent criteria for a CFS response (with response now defined as improvement of ≥ 3 points in CFS and an improvement by ≥ 30% in OSDI). For observed data, response rates in the Ikervis and vehicle arms were 21.4% and 8.5% respectively and for imputed data were 18.8% and 7.7% respectively. Again, this is a greater between-arm difference than when using CFS ≥ 2 to define response: 12.9% versus 5.5% using imputed data or 11.1% versus 8.4% when using observed data.

At 6 months, Figure B8 in the CS shows that the Ikervis arm showed a statistically significant decrease in HLA-DR (AUF) from baseline (-14554) as opposed to an increase in vehicle (+ 8399) (p = 0.021). Median HLA-DR (AUF) also decreased markedly over 12 months in both

patients treated with Ikervis throughout (-15945) and those who crossed over from vehicle at 6 months (-17147). This appears to demonstrate that Ikervis has an anti-inflammatory effect.

Tear film osmolarity was only assessed in selected centres where the test was available, i.e. a subset of the entire trial population. The post-hoc analysis of worst tear film osmolarity was performed in a further subset, patients with elevated tear film osmolarity at baseline. Hence the findings must be considered exploratory. After 6 months, the adjusted mean change in worst tear film osmolarity from baseline was -26.7 mOsms/L with Ikervis and -16.7 mOsms/L with vehicle (p = 0.048). Between months 6 and 12 of the trial, changes of -2.9 and -4.16 mOsms/L were observed in patients remaining on Ikervis and those switching from vehicle to Ikervis respectively.

Pooled data

In the subgroup of Sjögren's patients with severe DED (CFS = 4 and OSDI ≥ 23, n = 130), the rate of CFS-OSDI responders (patients with an improved CFS ≥ 2 and an improved OSDI ≥ 30%) was statistically significantly higher (p = 0.028) for Ikervis (23.4%) than vehicle (9.4%). As the severe population investigated in SANSIKA was selected following post-hoc analyses in SICCANOVE, such a result is not unexpected.

4.3 Critique of the safety data

Safety data from the SANSIKA and SICCANOVE trials were presented in the CS. Data on types of AEs were also pooled from these two trials. The company states (page 133 of CS) that "pooled safety data [from SANSIKA and SICCANOVE] presents the advantages to offer a larger patient population to provide an improved precision of estimates and is justified by the fact that only one dose strength of the formulation is proposed i.e. 0.1%; and the patient population involved in these two studies is broadly comparable i.e. patients with moderate to severe DED." While the ERG concurs that this approach is normally the preferred method of reporting AEs, since only SANSIKA included only patients with severe DED and the excipients used in both trials differed, AEs reported in SANSIKA are arguably of greater importance. A summary of the pooled AE data by the ERG is included in Appendix 2 (section 10.2) of this report and a detailed breakdown of treatment-emergent AEs for SANSIKA is also presented here, in Table 25. The ERG notes that the proportions of patients with the types of treatment-emergent AEs reported in SANSIKA are similar to those in the pooled analysis. The ERG also notes that in SANSIKA, with the exception of severe ocular AEs and serious AEs (SAEs), the proportion of AEs was greater in the Ikervis arm than the vehicle arm and the proportion of AEs in patients treated with Ikervis only was greater at 12 months than 6 months. There were no deaths in either arm. In summary:

- After 6 months, treatment-related AEs were reported by 37.0% of patients treated with Ikervis compared to 21.1% in the vehicle arm; after 12 months the proportion rose to 45.5% in the Ikervis arm. Identical proportions of patients with AEs experienced treatment-related ocular AEs in the Ikervis arm at 6 and 12 months (in vehicle it was very similar, 20.0% at 6 months)
- The proportion of severe ocular AEs were similar in both arms of SANSIKA after 6 months (5.8% in Ikervis arm versus 5.6% in vehicle arm). After 12 months the proportion in the Ikervis arm rose slightly to 7.1%)
- Non-severe AEs in SANSIKA were reported in the CS to be managed by either temporary or permanent cessation of treatment and severe AEs by permanent cessation of treatment. After 6 months, AEs leading to treatment discontinuation were 13.6% in the Ikervis arm and 10.0% in the vehicle arm. The CS reports that over 12 months, treatment with Ikervis was discontinued due to treatment-related AEs by 20.1% of patients
- SAEs were reported in a higher proportion of patients in the vehicle arm (6.7% versus 3.9% in Ikervis arm) but only one SAE was considered to be treatment-related. This ocular SAE occurred in the vehicle arm
-

The CS reports that the most common AEs experienced by patients treated with Ikervis occurred mainly in the two following system organ classes: eye disorders and general disorders and administration site conditions. Eye irritation and eye pain were described in the CS as the most common AEs. These were described by the company as being usually

transitory and commonly occurring during instillation of the eye drops (i.e. instillation site pain and instillation site irritation). From an examination of the AE data reported in the CSRs, eye pain attributed to instillation appeared to be more common in SANSIKA than SICCANOVE with general eye pain, general eye irritation and instillation site irritation more common in SICCANOVE (Table 9). Reasons for the differences are unclear but given the company states the methodology used for recording AEs was comparable between the trials, the ERG speculates this may be attributable in part to the different excipients used in the trials; differences in disease severity in the two trials is also likely to be a factor as in more severe DED, eye drops can create transitory irritation. Indeed, during the clarification process, the company confirmed that a smaller proportion of severe ocular AEs were observed with the CKC excipient (6.2%) used in SANSIKA and ORA than with the BAK formulation (27.5%) used in SICCANOVE and another phase II trial.

Table 9 Key AEs highlighted by the company from SANSIKA and SICCANOVE†

Trial, N (n in Ikervis; n in vehicle)	**Ikervis**		**Vehicle**	
	Patients, n (%)	**Events, n**	**Patients, n (%)**	**Events, n**
Eye disorders				
Eye Irritation				
SANSIKA part 1, N = 244 (154; 90)	4 (2.6)	4	2 (2.2)	3
SICCANOVE, N = 492 (242, 250)	39 (16.1)	43	8 (3.2)	8
Pooled data, N = 736 (396, 340)	43 (10.9)	47	10 (2.9)	11
SANSIKA part 2, N = 154*	6 (3.9)	6	N/A	N/A
Eye pain				
SANSIKA part 1, N = 244 (154; 90)	1 (0.6)	1	4 (4.4)	5
SICCANOVE, N = 492 (242, 250)	17 (7.0)	22	9 (3.6)	10
Pooled data	18 (4.5)	23	13 (3.8)	15
SANSIKA part 2, N = 154*	2 (1.3)	2	N/A	N/A
General disorders and administration site conditions				
Site Irritation				
SANSIKA part 1, N = 244 (154; 90)	0	0	0	0
SICCANOVE, N = 492 (242, 250)	19 (7.9)	28	4 (1.6)	4
Pooled data	20 (5.1)	28	4 (1.2)	4
SANSIKA part 2, N = 154*	2 (1.3)	1	N/A	N/A
Site pain				
SANSIKA part 1, N = 244 (154; 90)	47 (30.5)	56	8 (8.9)	8
SICCANOVE, N = 492 (242, 250)	3 (1.2)	3	1 (0.4)	1
Pooled data	50 (12.6)	59	9 (2.6)	9
SANSIKA part 2, N = 154*	56 (36.4)	66	N/A	N/A

† AE data for SICCANOVE includes patients with moderate to severe DED and not only severe DED

* SANSIKA part 2 data is presented for patients who received Ikervis for 12 months (and excludes those who switched from vehicle to Ikervis at 6 months)

Source: Adapted from Table B21 of CS, Tables 56 and 59 of SANSIKA CSR and Table 5.3.2 of SICCANOVE CSR; the ERG notes that the total number of patients reported to have experienced site irritation in the pooled analysis over 6 months in the CS (20) exceeds the total number from summing the data in SANSIKA and SICCANOVE (19)

No safety data were reported for other formulations of CsA in the CS. However, the company states AEs observed with Ikervis were consistent with those reported in the literature with Restasis and other CsA formulations (page 138 of CS).

4.4 Critique of the health-related quality of life data

HRQoL data were only collected in the SANSIKA trial. Two measures were utilised: NEI-VFQ-25, an ophthalmic specific questionnaire, and EQ-5D, a generic health questionnaire. The ERG considers both questionnaires to be appropriate for measuring HRQoL. However, the ERG notes that the change from baseline data measured by the NEI-VFQ-25 questionnaire were derived from just less than half (49%) of all participants in the SANSIKA trial. Response rates were higher for change from baseline data in the EQ-5D summary index and EQ-5D VAS scores (80% and 78% respectively).

For the NEI-VFQ-25, mean ± SD composite score at baseline was relatively similar in both treatment groups (71.9 ± 15.7 for patients treated with Ikervis versus 74.0 ± 13.4 for patients treated with vehicle). The company states that similar baseline results were reported for the 12 individual scale scores. After 6 months there was no statistically significant difference between treatment arms in the mean change from baseline in the NEI-VFQ-25 composite score (+4.1 for patients treated with Ikervis and +4.0 for patients treated with vehicle). However, the company states that a trend was identified in terms of a greater improvement at 6 months for the ocular pain dimension in patients treated with Ikervis (+14.4) compared with those receiving vehicle (+10.0).

The EQ-5D mean ± SD summary index at baseline was similar in both treatment groups (0.66 ± 0.30 for patients treated with Ikervis and 0.66 ± 0.26 for patients receiving vehicle) as was mean ± SD EQ-5D VAS score (63.9 ± 19.2 for patients treated with Ikervis and 68.2 ± 17.0 for patients receiving vehicle). No statistically significant differences in the summary index or the EQ-5D VAS score between arms were reported at 6 months with no changes in the summary index or the EQ-5D VAS score over time being reported in either arm. The ERG notes that the change from baseline data in the summary index was similar in both arms (0.02 ± 0.25 in the Ikervis arm and 0.02 ± 0.21 in the vehicle arm); however the change from baseline data in the EQ-5D VAS score, although not statistically different, suggested an improvement over time in the Ikervis arm (+2.38 ± 19.27) unlike the vehicle arm (-1.55 ± 18.27).

4.5 Additional work on clinical effectiveness undertaken by ERG

As noted in section 4.2.1, a number of RCTs involving CsA have been published but were not included in the CS as they were not considered relevant to this appraisal. The company appears to consider that trials of other formulations of CsA are not relevant to the decision problem. Whilst the ERG disagrees with this view (since it considers other formulations of CsA to be relevant comparators), it does acknowledge that it is not possible to carry out reliable comparisons of trials of other CsA formulations with trials of Ikervis; certainly it is not possible to conduct a direct or formal indirect treatment comparison because the vehicle arms across trials are too heterogeneous. However, from the systematic review report conducted on behalf of the company,[38] and provided by the company as part of the clarification process, the ERG notes the following regarding presented CFS, OSDI and AE data for Ikervis and Restasis:

- The mean change in CFS in patients treated with Ikervis from baseline to end of treatment (24 weeks) was -1.81 in SANSIKA and -1.05 in SICCANOVE. For patients treated with Restasis the mean change from baseline to end of treatment in four studies (13 to 24 weeks)[46,49-51] ranged from -0.27 to -1.52
- The mean change in OSDI in patients treated with Ikervis from baseline to end of treatment (24 weeks) was -14.41 in SANSIKA and -11.81 in SICCANOVE. For patients treated with Restasis, in two studies[49,51] the mean change from baseline to end of treatment (12 to 13 weeks) ranged from -3.03 to -6.20 with Restasis 0.05% and -8.69 to -15.19 for higher concentrations (0.1% to 0.4%)
- The overall incidence of patients experiencing treatment-related ocular AEs over 24 weeks ranged from 34.6% in the Ikervis arm of SICCANOVE to 37.0% in the Ikervis arm of SANSIKA. Only one trial reported treatment-related AE incidence for Restasis[46] which over 24 weeks ranged from 25.3% (Restasis 0.05%) to 29.1% (Restasis 0.1%)
- The overall incidence of patients withdrawing treatment due to AEs in the Ikervis arm ranged from 9.9% in SICCANOVE to 13.6% in SANSIKA (24 weeks). For patients treated with Restasis, in three studies[46,49,50] the incidence ranged from 6% to 10% (13 to 24 weeks)

Taken together these clinical comparisons suggest that Ikervis compares favourably with Restasis, albeit with a possible increase in AEs. However, the ERG stresses that these comparisons are crude and the suggested conclusions should not be considered as robust, particularly given trial heterogeneity in terms of defining the severity of DED, length of follow-up and, in some instances, baseline characteristics. Furthermore, the systematic review report[38] emphasises that reporting of AEs across studies was limited.

4.6 Conclusions of the clinical effectiveness section

The company is seeking a recommendation for Ikervis (CsA 0.1%), which is a new formulation of CsA not currently available in clinical practice. Evidence is presented from the SANSIKA trial which is considered pivotal (and from which evidence is derived to inform the cost effectiveness analysis) and from the SICCANOVE trial (which the company considers to be supportive). However, evidence from the SICCANOVE trial is of limited relevance to the decision problem as no more than 17% of patients in this trial had severe DED (as per the definition used in the SANSIKA trial) and the vehicle contained BAK as opposed to CKC. However, post-hoc findings in patients with severe DED from SICCANOVE were appropriately used to inform pre-specified analyses in the pivotal SANSIKA trial.

The SANSIKA trial measures efficacy in terms of signs and symptoms, AEs and HRQoL, all of which are important outcomes to clinicians and patients. It also appears to be at low risk of bias and generalisable to clinical practice in England in terms of patient characteristics. However the primary outcome (a composite endpoint of CFS and OSDI response) was not met and only two pre-specified secondary outcome measures showed a significant difference for Ikervis compared with vehicle. Improvements were reported over time for all efficacy outcomes in both arms. This suggests that vehicle may deliver some therapeutic benefit but it is not clear whether the improvements occurred as a result of the vehicle, as a result of concomitant AT use, or as a combination of both vehicle and AT. Notwithstanding the ERG's reservations about the relevance of the primary outcome (due to a lack of prior studies validating this composite endpoint), statistical analyses demonstrate that the superiority of Ikervis compared with vehicle has not been demonstrated. Furthermore, no difference in HRQoL was found between the trial arms. However, the ERG considers the safety profile of Ikervis to be acceptable.

As Ikervis vehicle is not commercially available, the ERG takes the view that a more appropriate comparison would be between Ikervis and other CsA formulations currently used (off-label) in clinical practice. These include the CsA 0.1% eye drops, which have been approved for use in the USA (Restasis), other CsA eye drops (2%) and the Optimmune ointment (CsA 0.2%). Unfortunately, there are no trials comparing Ikervis with these CsA formulations and because of differences in vehicles used in each formulation, a lack of a common comparator also prevents the conduct of a robust indirect treatment comparison.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by Santen GmbH in support of the use of CsA for the treatment of severe keratitis in adult patients with DED that has not improved despite treatment with tear substitutes. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic copy of their economic model that was developed in Microsoft Excel.

5.2 ERG comment on company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company undertook a search to identify publications reporting the cost effectiveness or cost utility of the use Ikervis by people with DED whose disease had not adequately responded to tear substitutes.

Details of the search strategies employed by the company are included in Appendix 10 of the CS. Medline (via OVID SP), Medline R-In Process (via OVID SP), Econ-Lit (via OVID SP) and EMBASE (via OVID SP) searches were undertaken. Additionally, searches of the NHS Economic Evaluation Database (NHS EED) and the Cochrane Database of Abstracts and Reviews of Effects (DARE) were performed. The time horizon for the searches was database inception (Medline 1946; Embase 1974; EconLIT 1898; NHS EED 1960) to 15th July 2014.

5.2.2 Eligibility criteria used in study selection

The inclusion criteria used in the company's study selection are presented in Table 10. The ERG is satisfied that these criteria are relevant to the decision problem.

Table 10 Economic evidence search inclusion criteria used by the company

	Inclusion criteria
Patients	People with severe dry eye disease whose disease has not adequately responded to tear substitutes
Subgroups	None
Interventions	Ikervis
Study type	Cost-effectiveness and cost-utility analyses
Country	UK, US and EU5
Year of publication	2012 onwards

Source: Table B22 of the CS

5.2.3 Included and excluded studies

No relevant studies were identified by the company.

5.3 ERG critique of the company's literature review

The ERG is satisfied with both the company's search strategy and their review inclusion criteria, and is confident that the company did not miss any relevant published papers. The ERG notes that since CsA has not yet received a full marketing authorisation from the EMA for the treatment of DED, the lack of economic evaluations of relevance to the decision problem is not unexpected.

5.4 Summary and critique of company's submitted economic evaluation by the ERG

5.4.1 NICE reference case checklist

Table 11 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial
Comparator(s)	Alternative therapies routinely used in the NHS	No – there is no approved comparator in the UK. The economic model compared Ikervis plus AT with AT alone
Perspective costs	NHS and Personal Social Services	Only NHS costs were included in the model
Perspective benefits	All health effects on individuals	Health effects to the individual are captured via QALYs
Form of economic evaluation	Cost effectiveness analysis	Cost effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	Lifetime horizon was used (30 years)
Synthesis of evidence on outcomes	Systematic review	A systematic review was undertaken but revealed no relevant studies. Outcome evidence was extracted from the SANSIKA trial, with the efficacy of AT alone assumed to be the same as vehicle
Outcome measure	Quality adjusted life years (QALYs)	QALYs were used which is appropriate
Health states for QALY	Described using a standardised and validated instrument	EQ-5D was used, with data collected from the SANSIKA trial
Benefit valuation	Time-trade off or standard gamble	Time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	The company report that UK preference data were used. However, the source quoted in their response to a clarification question (Rubin 2011[70]) does not contain preference data for people with DED
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs were discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis	Deterministic, scenario and probabilistic sensitivity analyses were undertaken by the company

AT = artificial tears; DED = dry eye disease; EQ-5D = EuroQol-5 dimension; QALY = quality adjusted life year

5.4.2 Drummond checklist

Table 12 Critical appraisal checklist for the economic analysis completed by ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	No	The question was well defined but impossible to answer due to the lack of data relating to an appropriate comparator
Was a comprehensive description of the competing alternatives given?	Partial	There is some discussion in the clinical sections of the CS
Was the effectiveness of the programme or services established?	No	In terms of the composite primary endpoint analysis of SANSIKA trial data showed no significant difference between the intervention and the comparator. Results from an adjusted, post-hoc, definition of the primary outcome were used in the model
Were all the important and relevant costs and consequences for each alternative identified?	Mostly	The model includes a number of bold assumptions and simplifications
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Yes	-
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs were calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

CS = company submission; ICER = incremental cost-effectiveness ratio

5.4.3 Model structure

A schematic of the company's model is provided in the CS and reproduced in Figure 1. It is a state transition (Markov) model with a cycle length of 3 months and is largely populated with data from the SANSIKA trial. All patients enter the model in the 'treatment induction' health state where they receive Ikervis plus AT or AT alone. They remain in this state for 6 months, after which they move to either the 'treatment responders' health state or the 'non-responders' health state. To be classified as a responder, an OSDI improvement from baseline of at least 30% as well as a CFS improvement from baseline of three or more is required. Patients in the 'treatment responders' health state remain in that state and continue on their assigned therapy until that therapy is no longer efficacious. When therapy is no longer efficacious patients move to the non-responders health state. Patients in the non-responders health state either stay in that state (receiving AT alone) or temporal punctal

plugs are trialled. Those patients who respond well to the temporal punctal plugs progress to having that treatment made permanent and progress to the 'Post plugs' state.

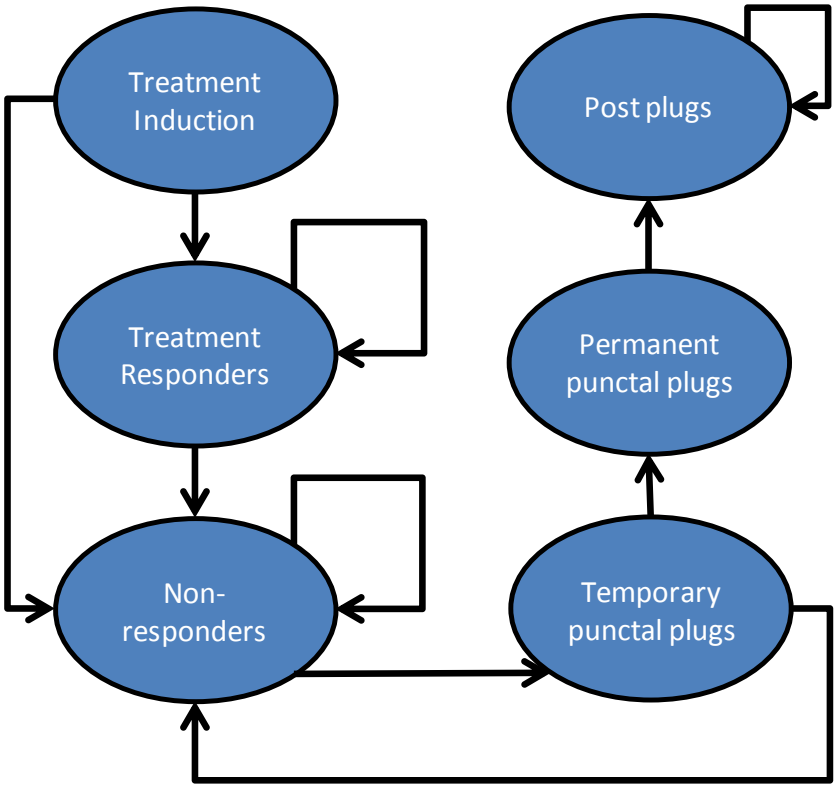

Figure 1 Schematic of company's model

Source: Figure B10 of the CS

5.4.4 Population

The company states (on page 145 of the CS) that the model population is based on the cohort of patients that participated in the SANSIKA trial, namely adult patients with DED and severe keratitis whose disease has not adequately responded to tear substitutes.

5.4.5 Interventions and comparators

This appraisal compares the use of Ikervis plus AT with AT alone (standard care). The intervention has been implemented in the model in line with its expected marketing authorisation, i.e. 1 drop of Ikervis once daily. The profile of AT usage was taken from a paper written by Clegg et al[19] in which it was reported that in the UK, 57% of patients with severe DED are prescribed polyvinyl alcohol (Liquifilm Tears), 50% are prescribed carbomers (Viscotears) and 50% are prescribed paraffin.

5.4.6 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. However, it should be noted that the model does not include any Personal Social Services costs. The time horizon is set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal,[71] both costs and outcomes are discounted at 3.5%.

5.4.7 Treatment effectiveness and extrapolation

Treatment response rates (first 6 months)

SANSIKA trial data were used to model response to both Ikervis and vehicle at 3 and 6 months. A summary of the SANSIKA response to treatment data that were used to calculate cycle response rates is presented in Table 13.

Table 13 Summary of response to treatment during first 6 months of the SANSIKA trial

	Ikervis	Vehicle
Number of patients in study arm	154	91
Number of patients with data analysed	131	82
3 month response		
SANSIKA trial response criteria*	22.5%	13.5%
Post-hoc analysis response criteria**	16.2%	7.7%
6 month response		
SANSIKA trial response criteria*	32.8%	24%
Post-hoc analysis response criteria**	18.8%	7.7%

* CFS improvement ≥ 2, OSDI change ≥ 30% (observed data)

** CFS improvement ≥ 3, OSDI change ≥ 30% (The data set from which 3 month response figures have been calculated but the 6 month response figures appear to have been calculated using imputed data)

AT = artificial tears

Source: Section 7.3 of the CS

Treatment continuation rates (post 6 months)

The SANSIKA withdrawal rate (observed data) between 6 and 12 months was used to estimate the cycle probability of ceasing Ikervis plus AT therapy. The company's calculations result in the probability of stopping treatment in each cycle being 5.6%.

Data from the first 6 months of the SANSIKA trial for patients in the vehicle arm were used as a proxy to calculate the probability of withdrawing from AT treatment. The company's calculations result in the probability of stopping treatment in each cycle being 6.3%.

Temporary punctal plugs and permanent punctal occlusions

The company assumed that the annual rate of punctal plug usage was 0.01 surgical procedures, of which punctal plugs accounted for 94%. This assumption is in line with figures reported by Clegg et al[19] who report punctal plug usage of less than 0.01 per person with DED per year. The company notes that a systematic review by the Cochrane Collaboration[72] found limited evidence on the efficacy of punctal plugs and that they have, therefore, assumed that 10% of those who have a temporary punctal plug have their treatment made permanent. Those who are unresponsive to a temporary punctal plug have the plug removed and are prescribed AT. Permanent punctal occlusions are assumed to be 100% efficacious.

Mortality

Since DED has no effect on mortality, patients are assumed to have the same mortality rate as the general population and, the company, therefore, has used Office for National Statistics mortality rate figures in their model.[73]

Response rates used in the company's model

It is assumed that all non-mortality related transition probabilities for responders and non-responders are constant over time. A summary of the response rates used in the company's model is presented in Table 14.

Table 14 Response rates used in the company's model

Variable	Cycle rate	Source
Ikervis + AT 3 month response	0.162	SANSIKA trial data
Ikervis + AT 6 month response	0.188	SANSIKA trial data
AT 3 month response	0.077	SANSIKA trial data
AT 6 month response	0.077	SANSIKA trial data
Non responder to temporary punctal plug transition	0.024	Assumption
Temporary to permanent punctal plug transition	0.1	Assumption
Ikervis + AT cycle failure	0.056	SANSIKA trial data
AT cycle failure	0.063	SANSIKA trial data

Source: Table B26 of the CS

5.4.8 Health-related quality of life

The relative impact of severe DED on HRQoL, compared to the general UK population, is assumed to be constant over time and is conditional on whether the patient is classified as a responder or a non-responder. The utility values used in the model have been estimated from EuroQol EQ-5D questionnaire data collected at baseline and at 6 months in the SANSISKA study and are displayed in Table 15.

Table 15 Utility values used in the company's model

CFS-OSDI response*	Utility value	Standard error
Response	0.0736	0.0343
Non-response	-0.0040	0.0299

* The composite primary endpoint in the SANSIKA trial is the CFS-OSDI response, i.e. an improvement of ≥ 2 points from baseline in CFS and an improvement of ≥ 30% from baseline in symptoms (using the OSDI) after 6 months of treatment

Source: Table B33 of the CS

The company undertook a systematic literature review to identify relevant HRQoL data. They concluded that there are no published studies which capture and report EQ-5D utilities in a population that is similar to that recruited to the SANSIKA trial. The company observes, however, that the utility benefit results from SANSIKA data are similar to the published incremental response utilities reported by Schiffman et al.[74]

The company has assumed that responders to punctal plugs gain the same incremental utility benefit as responders to active treatment.

Adverse events

The company reports that severe treatment-related AEs will lead to discontinuation of treatment and are implicitly included in the model (over 12 months in the SANSIKA trial treatment with Ikervis was discontinued due to treatment-related AEs in 20.1% of patients). In addition, the company reports that the impact of other treatment-related AEs are not included in the model as most are mild and transient and, therefore, have a negligible impact on HRQoL and do not require treatment. The ERG notes that in the SANSIKA trial only one of the 22 SAEs was considered by the investigator to be definitely treatment-related (a severely reduced visual acuity in one patient in the vehicle arm).

5.4.9 Resources and costs

Intervention (Ikervis) use and cost

The company has assumed that the entire cohort has both eyes treated (in the SANSIKA trial the average number of eyes treated was 1.97) with one drop of Ikervis per day. All patients receive treatment for 6 months. Responders receive treatment until they either cease to respond to treatment or they die.

AT usage and cost

The company has assumed that the baseline usage of AT in the SANSIKA trial reflects UK clinical practice. In this study the average number of drops per eye per day was 13.24 and 16.54 drops in the Ikervis and vehicle arms respectively. The company has taken a simple average (14.89) and used this in both arms of the model.

The company highlights that interpretation of the change in AT usage at 6 months, from baseline, is challenging. At 6 months in the SANSIKA trial the average number of drops per day in the Ikervis arm was 12.68 (6.34 drops per eye, two eyes treated) and the average number in the vehicle arm was 14.64 (7.32 drops per eye, two eyes treated). These figures were used in the company's model to represent AT usage for the Ikervis plus AT and AT only model arms respectively.

Non-responders are assumed to cease therapy and revert back to standard care alone. The company assumes, for these patients, that the usage of AT will revert to the level of usage observed at baseline in the SANSIKA trial, i.e. patients will require 29.78 drops per day (14.89 drops per eye, two eyes treated).

The insertion of a permanent punctal occlusion is assumed to be 100% successful and patients who have had this operation are assumed to no longer require AT. Patients' use of AT is also assumed to be zero during the period when a temporary punctal plug is inserted.

The company considers that the latter assumption is conservative. However, clinical advice to the ERG is that these assumptions are not robust as punctal plug surgery is not 100% successful and that surgery and plugs reduce, rather than eliminate, AT usage.

The levels of different types of AT usage (extracted from Clegg et al[19]) and their costs are displayed in Table 16. Monthly intervention and AT costs are shown in Table 17.

Table 16 Usage and costs of ATs

Component	AT usage[19]	Units per pack	Pack cost	Unit cost	Source[75]
Polyvinyl alcohol (single use Liquifilm Tears)	57%	30	£5.35	£0.18	BNF
Carbomers (single use Viscotears)	50%	30	£5.42	£0.18	BNF
Paraffin (liquid paraffin 10%, wool fat 10% in yellow soft paraffin, 4g)	50%	1	£3.25	£3.25	BNF

AT = artificial tears
Source: Table B36 and Table B37 of the CS

Table 17 Monthly intervention and comparator costs

Items	Ikervis + AT	AT	Non-responders
Technology cost	£72	£0	£0
AT usage	£38.67	£44.40	£88.63
Total (per month)	£110.67	£44.40	£88.63

Source: Table B39 of the CS

Punctal plug cost

In the absence of any information on the cost of punctal plug, the company has estimated the cost based on two Healthcare Resource Group (HRG) tariffs. The tariff values have been extracted from the 2013 version of the NHS Schedule of Reference costs[38] (NHS SRC) and it has been assumed that all procedures are carried out as day cases on an elective basis. The cost calculations are presented in Table 18.

Table 18 Calculation of estimated cost of inserting a temporary or permanent punctal occlusion

HRG (2012-13)	Description	Value	FCEs	Source
BZ10C	Minor orbits or lacrimal procedures, 19 years and over, with cc score 2 +	£657	422	NHS SRC 2013[76]
BZ10D	Minor orbits or lacrimal procedures, 19 years and over, with cc score 0-1	£613	4,712	NHS SRC 2013[76]
Weighted average		£616.62		
Value after inflation (estimated at 2%)		£628.95		

FCE = finished consultant episode; HRG = healthcare resource group; NHS SRC = NHS Schedule of Reference Costs
Source: Table B34 of the CS

Health state costs

Monthly health state costs included in the company's model are summarised in Table 19.

Table 19 Monthly health state costs

Health states	Type of expenditure	Value
Ikervis + AT responder	Technology	£110.67
AT responder	Technology	£44.40
Non-responder (all interventions)	Technology	£88.63
Temporary punctal plugs	Procedure cost	£628.95
Permanent punctal occlusion	Procedure cost	£628.95
Post-surgery	None	£0

AT = artificial tears
Source: Table B40 of the CS

Administration and pharmacy costs

The company's model does not include any administration or pharmacy costs. Furthermore, no monitoring costs are included in the model as the company has assumed that all patients (irrespective of type of treatment) receive the same levels of monitoring.

Adverse event costs

The company reports that costs associated with treatment-related AEs are not included in the model as most are mild and transient and, therefore, do not require treatment. In addition, the company reports that punctal plug is a low risk procedure with a low procedure rates in the UK, and that as the cost of AEs associated with this procedure are negligible no such costs are included in their model.

5.4.10 Cost effectiveness results

Predicted (per patient) resource use costs included in the company's model are presented in Table 20.

Table 20 Predicted resource use by cost category

Outcome	Ikervis + AT	AT alone	Incremental
Trial 0-3 months	£331	£133	£198
Trial 3-6 months	£331	£133	£198
Maintenance	£1,080	£160	£920
Temporary punctal plugs	£358	£367	-£9
Permanent punctal occlusion	£35	£36	-£1
Non-responders	£21,406	£21,942	-£535
Total (undiscounted)	£23,542	£22,771	£771
Total (discounted)	£15,997	£15,283	£713

AT = artificial tears

N.B. Post-hoc response definition, i.e. improvement of ≥ 3 points from baseline in CFS and an improvement of ≥ 30% from baseline in symptoms (using the OSDI) after 6 months of treatment

Source: Company's model ("Results (H2H)" sheet)

The incremental cost effectiveness results generated by the company's economic model are presented in Table 21. The model results show that, compared to AT alone, use of Ikervis plus AT leads to a lifetime additional cost to the UK NHS of £713 per patient. It also offers an additional 0.04 QALYs per patient and the resultant ICER for this comparison is £19,156 per QALY gained.

Table 21 Company's base case cost effectiveness results: Ikervis plus AT versus AT

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
AT	£15,283	9.71			
Ikervis + AT	£15,997	9.74	£713	0.037	£19,156

AT = artificial tears; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

N.B. Post-hoc response definition, i.e. improvement of ≥ 3 points from baseline in CFS and an improvement of ≥ 30% from baseline in symptoms (using the OSDI) after 6 months of treatment

Source: Table B45 of the CS

5.4.11 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out a wide range of deterministic sensitivity analyses. Results for the ten parameters showing the greatest variability for the comparisons of Ikervis plus AT versus AT are shown in Figure 2. The most influential variable was response utility which, when the mean value (0.738) minus two standard errors (i.e. 0.669) was used, increased the ICER for the comparison of Ikervis plus AT with AT alone to £165,654 per QALY gained. All the analyses that increase the company's predicted ICER per QALY gained to a value over £25,000 are shown in Table 22.

Table 22 Sensitivity analyses that result in an ICER per QALY gained of over £25,000

Parameter modification	Base case value	Sensitivity analysis value	ICER per QALY gained
Base case ICER			£19,156
Response utility	0.738	0.669	£165,654
Ikervis acquisition cost	£72	£100	£29,906
Ikervis total health state costs	£110.67	£132.8	£27,651
Ikervis 6 month response probability	0.188	0.15	£26,318

ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year
Source: Table B46 of the CS

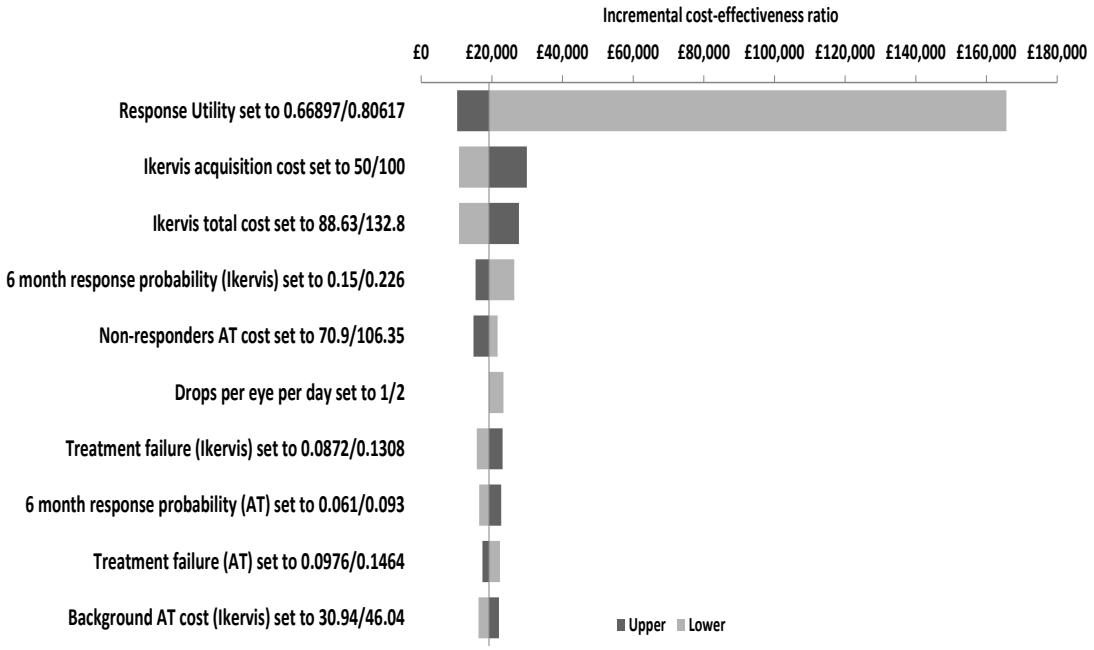

Figure 2 Most influential deterministic sensitivity analyses

AT = artificial tears
Source: Figure B11 of the CS

Probabilistic sensitivity analyses

The company undertook probabilistic sensitivity analysis (PSA) to derive the mean ICERs per QALY gained for Ikervis plus AT versus AT. PSA was carried out using 1000 iterations of the cost effectiveness model.

The probabilistic ICER for Ikervis plus AT versus AT is £18,835 per QALY gained, which is £321 less than the corresponding deterministic ICER (£19,156 per QALY gained). The PSA results show that, compared with AT alone, the probability of Ikervis plus AT being cost effective is 46.4% at a threshold of £20,000 per QALY gained and 70.7% at a threshold of £30,000 per QALY gained.

The company advises that a number of the simulations generated incremental benefits that were very close to zero, meaning that the probabilistic results are unstable and should be interpreted with caution. The cost effectiveness plane and cost effectiveness acceptability curve (CEAC) for this comparison are shown in Figure 3 and Figure 4 respectively.

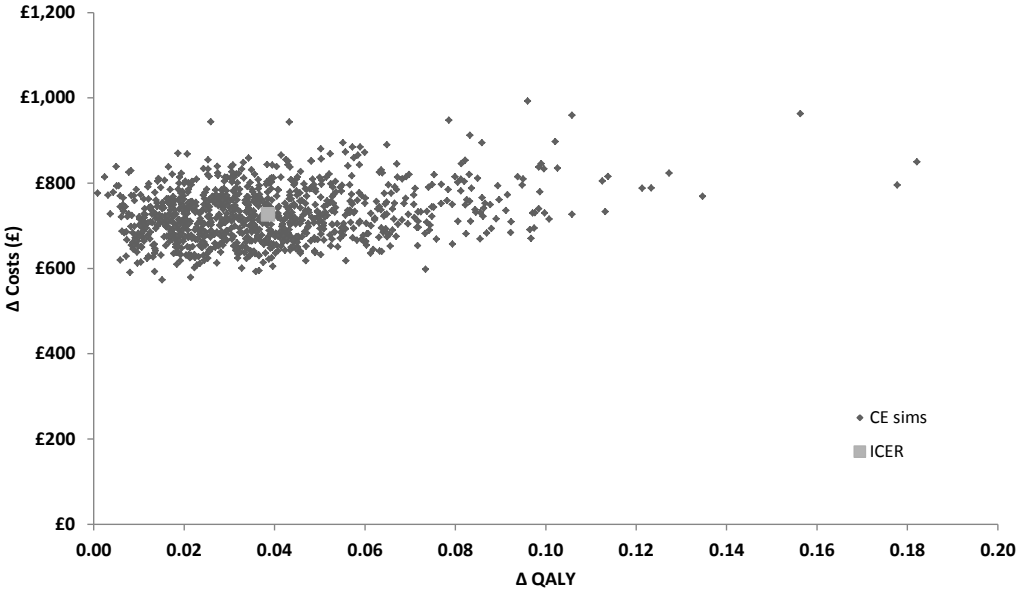

Figure 3 Cost effectiveness plane

CE = cost effectiveness; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year
Source: Figure B12 of the CS

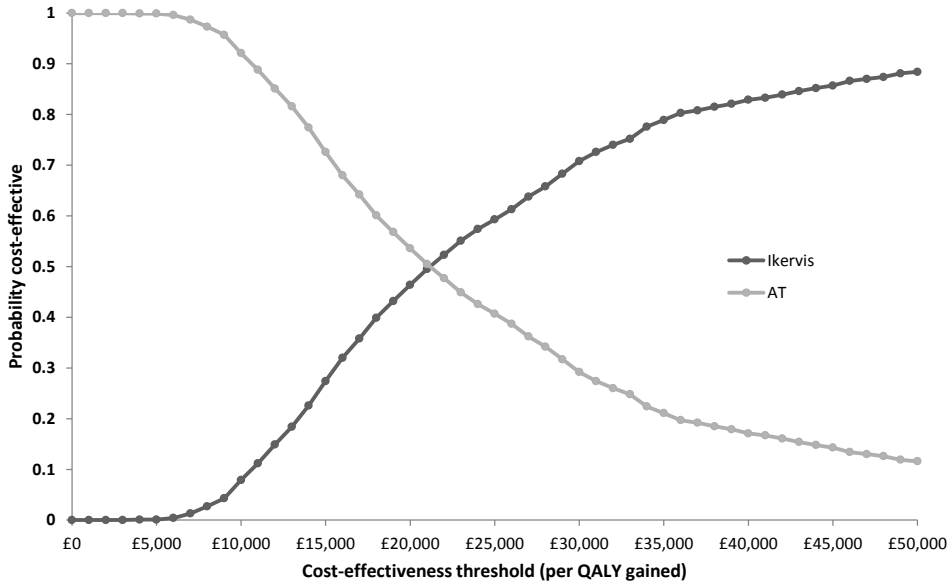

Figure 4 Cost effectiveness acceptability curve (CEAC)

AT = artificial tears; QALY = quality adjusted life year
Source: Figure B13 of the CS

Scenario analyses

The company also undertook a series of scenario analyses. The key findings from these analyses are summarised in Table 23.

Table 23 Key findings from the scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
Base case	£713	0.037	£19,156
Primary endpoint improvement criteria (CFS ≥ 2, OSDI ≥ 30%)	£1,145	0.034	£33,291
Alternative approaches to deriving response stratified utility values	£713	0.029	£24,765
3 month (rather than 6 month) trial period	£496	0.026	£18,739
	Findings		
Alternative utilities of responders to treatment	The company determined that Ikervis becomes cost effective at a threshold of £30,000 per QALY gained at utilities for responders of about 0.71 (i.e. an incremental gain for responders of 0.05)		
Time horizon	The company found that the model is insensitive to time horizons longer than 10 years		
Number of affected eyes	A linear relationship is observed with the cost-effectiveness of Ikervis decreasing to £23,290 per QALY when only one eye is treated		

CFS = corneal fluorescein staining; ICER = incremental cost effectiveness ratio; OSDI = Ocular surface disease index; QALY = quality adjusted life year

Source: CS pages196 to 198

5.4.12 Model validation and face validity check

The company reports that the conceptual model structure was reviewed and approved by clinicians familiar with the underlying condition. In addition, the model underwent rigorous technical validation by senior modellers who had not been involved in the original model construction.

5.5 Detailed critique of the company's economic model

5.5.1 Is the submitted economic model relevant to the decision problem?

The decision model submitted by the company is based on clinical evidence derived predominantly from the SANSIKA clinical trial which compared treatment with Ikervis to treatment with similar eye drops based on the same formulation used in Ikervis but excluding CsA (i.e. 'vehicle' only). This trial design was intended to demonstrate superior incremental efficacy attributable to the action of CsA.

However, the results from SANSIKA cannot be used directly to inform an economic evaluation because the comparator (vehicle) is not commercially available and, therefore, its use cannot be considered as current clinical practice in the NHS. Advice received by the

ERG indicates that for patients with established persistent severe DED with keratitis there are three medical options in current UK use: conventional preservative-free artificial tear eye drops, or CsA formulations in the form of either eye drops or ointment. The SANSIKA trial results cannot be used to inform an evidence-based comparison with any of these treatment options because there are no clinical trials which assess the relative efficacy of the SANSIKA vehicle compared with any of the currently used treatment options.

In the absence of a coherent evidence trail linking Ikervis to current CsA treatments, the only valid economic comparison available is a cost minimisation analysis i.e. to assume that all CsA based treatments are of equivalent efficacy, are associated with similar AEs and incur similar administration, prescribing and monitoring costs. The ERG acknowledges that such an assumption is open to criticism. However, if this approach is adopted, the comparison reduces to selecting the option available to the NHS with the least acquisition cost. Information provided to the ERG suggests that the following formulations are available at the following typical monthly costs:

- Restasis (0.05% CsA drops) £119.75
- Optimmune (0.2% CsA ointment) £55.24
- 2% CsA drops £47.24

On the basis of cost minimisation, Ikervis (£72 per month) is less costly than Restasis, but more costly than other CsA formulations currently used in clinical practice.

N.B. For reasons outlined in section 5.5.1, the ERG does not consider that the evidence available is sufficient to support a valid cost effectiveness analysis of Ikervis versus currently prescribed UK treatment options for severe DED. Although the following sub-sections of this report provide details of issues identified by the ERG as being of concern with the submitted economic model, the content should not be understood to be any expression of support for the validity of the model or the results obtained from it.

5.5.2 How the model generates health gain

A treatment may result in health gain in two ways in a decision model; through promoting extended survival or by improving the quality (or utility) of remaining life years. The company does not suggest that Ikervis offers any advantage in terms of life expectancy, so any health gain can only arise as a result of improved health-related utility.

However, the findings of the SANSIKA trial for the EuroQol EQ-5D utility score (p = 0.920) and VAS score (p = 0.839) indicate no statistically significant differences between the trial arms in the standard utility measures recommended in the NICE Methods Guide.[71] Neither do the results from the condition-specific NEI-VFQ-25 quality of life questionnaire indicate statistically significant differences overall, nor for any of its components.

The only statistically significant utility difference identified from the SANSIKA trial relates to the mean EQ-5D scores between patients with a defined response after 6 months treatment, and those without a response, pooled across both trial arms. For this result to lead to a health gain in the decision model it is applied to the proportions of trial patients in each arm with a defined response to treatment.

The definition of response used in the company base case analysis is not derived from the SANSIKA primary endpoint (based on an improvement in CFS score of at least 2 points) which did not demonstrate statistical significance, but from a post-hoc analysis restricting response to an improvement in CFS of at least 3 points. As a consequence, the company case for treatment-related health gain rests crucially on the post-hoc response rate analysis. Thus the two sets of parameter values which determine the extent of health gain (QALYs) in the submitted model are the differential response rates in the post-hoc analysis, and the estimated difference in mean EQ-5D values for patients experiencing a response to Ikervis treatment compared with those showing no response.

5.5.3 Population heterogeneity

The trial population includes a diversity of patients from those diagnosed with DED more than 31 years ago to some diagnosed less than 3 months ago. This raises the issue of heterogeneity within the population, and how this may influence the proportion of treated patients achieving a response (as defined in the SANSIKA trial). It is noticeable in the trial results that responses are confirmed in both treatment arms, but that the rate trends initially diverge and then stabilise so that after 3 months very little additional benefit occurs in either trial arm. One possible explanation for these results would be that a significant proportion of trial patients who were only recently diagnosed when entering the trial may have less established DED, i.e. DED that is more amenable to spontaneous improvement within the 6 month duration of the trial. In order to test this hypothesis and its possible impact on the decision problem, the ERG requested additional analyses of the SANSIKA trial data split between patients with short and long-term DED. Approximately 10% of SANSIKA patients were diagnosed no more than 2 years prior to randomisation. For these patients in the Ikervis trial arm there was no significant difference in response rate at 6 months using either definition of response ($p = 0.41$ for the trial definition, and $p = 0.98$ for the post-hoc definition). However, patients in the vehicle trial arm, diagnosed recently (≤2 years) showed response rates nearly double those experienced by similar patients receiving Ikervis treatment. The patient numbers involved are too small to draw definite conclusions, but it appears likely that more recently diagnosed patients may be amenable to important short-term improvement in their condition, delaying the need to escalate to medications containing CsA.

5.5.4 Age, sex and mortality

The company model assumes that all patients begin treatment at age 61 and that there are equal numbers of men and women. However, the trial population is predominantly female (85.3% overall) and there is a very wide age range at baseline (22 to 87 years). Since population mortality rates vary greatly by both age and sex, the company model is necessarily naïve and inaccurate if costs and outcomes are projected for up to 30 years. The correct method is to carry out modelling for each age group and sex combination, combining the results to obtain a weighted average result. The ERG has implemented a simple Visual Basic macro to perform this procedure which, when applied to the base case analysis using the SANSIKA trial population structure, increases the estimated ICER from £19,156 to £19,382 per QALY gained. The impact of this amendment varies depending on the scenario selected, and therefore unadjusted and adjusted ICERs are presented in the summary tables for each model amendment/scenario.

5.5.5 Effect of treatment response on EQ-5D utility values

Detailed examination of EQ-5D results from the SANSIKA trial indicates that there appears to be an advantage in terms of the average utility for responding patients compared with non-responders, whichever definition of response is used. The company approach to modelling the utility effect of response to treatment is based on an assumption that the improvement in HRQoL is not influenced by the treatment given, so that EQ-5D data are pooled across both trial arms. However, examination of the trial results indicates that a larger utility benefit is received by patients responding to treatment with the vehicle drops, than those who responded to Ikervis treatment (+ 0.038 using the trial definition of response, or + 0.049 using the post-hoc definition). The effect of using the pooled utility results in the model is to eliminate the potential impact of any differences in patient experience due to the characteristics of the randomised treatment. When separate trial-based utility values are applied, the ICER for the company's base case analysis (post-hoc response definition) increases by £5,317 per QALY gained, and Ikervis is dominated by the vehicle if the trial definition of response is used (i.e. Ikervis is more expensive and yields fewer QALYs). The most likely reason for the observed differences in utility between the treatments is that the additional AEs experienced in the Ikervis-treated patients (most related to instillation pain or discomfort), cause a reduction in the advantage that would otherwise accrue to patients reported to have achieved a response to treatment. This ERG amendment therefore compensates for the absence of any mechanism in the company model for the effects of AEs on patients.

5.5.6 Treatment discontinuation rates

The SANSIKA CSR[36] shows that discontinuations for any reason (16.2% versus 12.2% page 9) are higher in the Ikervis group. Also, treatment-related AEs leading to discontinuation are higher in Ikervis-treated patients (13.6% vs 10.0% Table S4 of SANSIKA CSR). The model per-cycle probabilities for continuing in treatment beyond the trial are estimated from trial data over different time periods (6 to12 months for Ikervis and 0 to 6 months for the vehicle) and indicate lower failure rates for Ikervis than vehicle (10.9% versus 12.2%). Applying the CSR values from the first 6 months to both model arms increases the ICER from £19,156 to £29,980 per QALY gained.

In response to a request from the ERG, the company provided Kaplan-Meier analyses for treatment discontinuation events in the SANSIKA trial data. The results are illustrated in Figure 5, and indicate that there is a high rate of discontinuation in the Ikervis arm during the first month, but thereafter a stable rate is established, equivalent to 5.9% of patients per 3 months of exposure to Ikervis. Patients in the vehicle arm of the trial are less likely to

discontinue treatment (4.6% per 3 months), with no evidence of any initial excess of patients discontinuing. When these parameter values are applied to the company model the ICER increases to £25,020 per QALY gained; this is the ERG's preferred option.

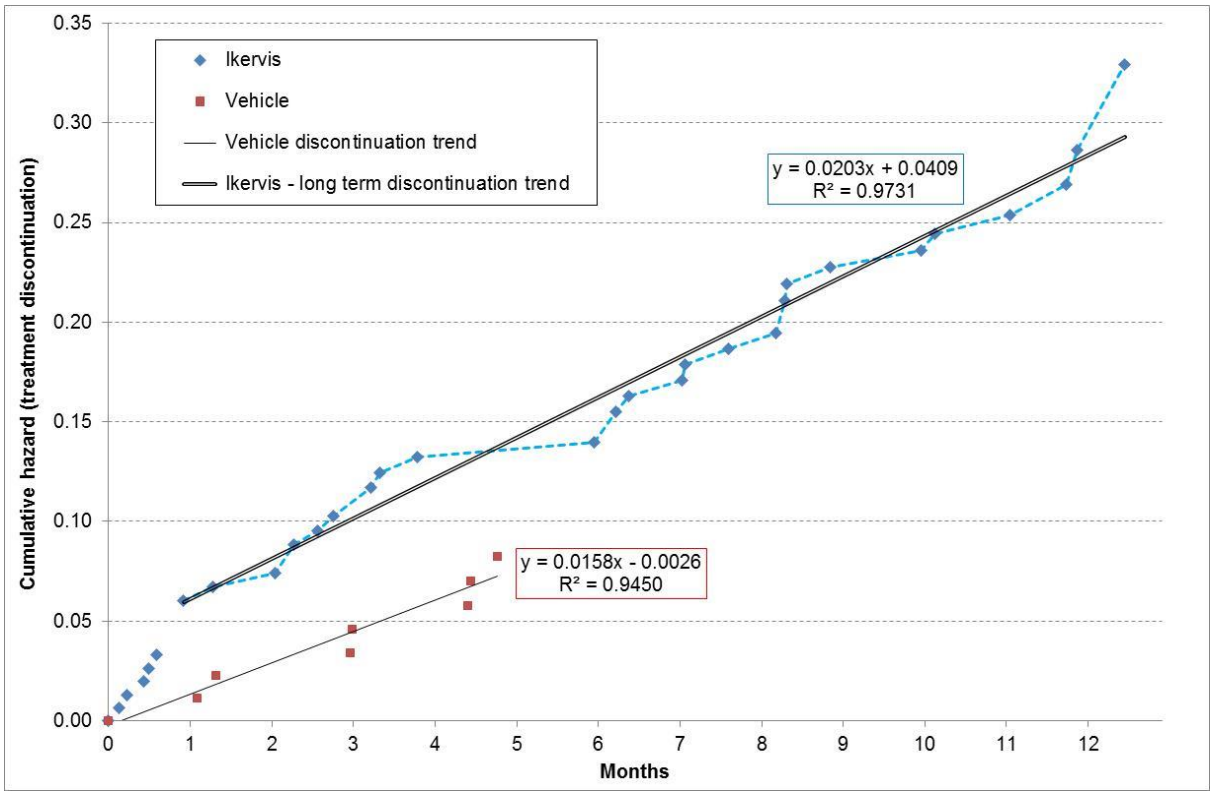

Figure 5 Cumulative hazard trends in SANSIKA trial discontinuation of treatment data

5.5.7 Artificial tear use error

The ERG has detected an error in calculating the frequency of AT use. The daily numbers of AT drops per eye were derived from the SANSIKA trial, and were accurately entered in relation to baseline use. However, the parameters for the trial period (6 months) were incorrectly applied at half the rate shown in the SANSIKA trial. In the long-term a single common value is used for all patients in the non-responder category, and this appears justified as usage in the two arms appears to converge at the end of the trial. Correcting this error results in an increase in the incremental cost of using Ikervis of £143 per patient, and leads to an increase in the estimated ICER of £3,836 per QALY gained.

5.5.8 Model coding errors

The ERG has detected an important problem which affects the estimation of both costs and outcomes (life years and QALYs) in the model. To replicate SANSIKA trial results, the company model calculates the proportions of the total cohort in four health states (alive/on trial treatment, alive/on continuation treatment, alive/non-responder, and dead) every 3

months. These values are then used to estimate the costs of treatment incurred and the number of life years and QALYs experienced in each 3 month cycle.

However, at the 6 month time point those patients still alive in the trial should be reclassified as 'responder' or 'non-responder' according to the 6 months trial efficacy assessment, and the resulting patient numbers become the starting values for estimating the distribution of surviving patients at the end of the third cycle (applying the risks of death and treatment failure during the third cycle). In fact, this reclassification is not applied in the submitted model until the end of the third cycle, altering the number of patients in all health states for the remainder of the model's time horizon (30 years). This problem is compounded by an additional error in which mortality rates are incorrectly offset by 3 months (i.e. using rates applicable to patients 3 months older), resulting in a compounded overstatement of estimated mortality over the 30 years of follow-up.

It is not possible for the ERG to correct these errors without a complex reworking of the central calculation worksheets of the model, which exceeds what can be carried out reliably within the time available. The alterations that would be required impact on all aspects of the model results (costs and outcomes) and it is not clear how the cost effectiveness estimates (ICERs) will be affected.

5.5.9 Treatment costs

The company modellers have applied treatment costs in the first 6 months (i.e. the trial period) assuming that treatment is prescribed for 3 months at the beginning of each cycle. This takes no account of the small risk of patients dying or discontinuing treatment during a 3 month cycle. On clinical advice the ERG has amended treatment costs throughout the time horizon of the model on the assumption that treatments are dispensed monthly, thus reducing in-period wastage. However, the model coding errors described in section 5.5.8 interact with this adjustment; altering treatment costs from quarterly to monthly relies on interpolating between the number of patients on treatment at the beginning and at the end of each cycle, and as these are incorrect in the submitted model for cycles 3 + this interpolation overstates treatment costs in cycle 3. Applying this amendment causes the incremental discounted costs to increase by £103, and the estimated base case ICER to increase by £2,760 per QALY gained.

5.5.10 Discounting logic

The submitted model applies discounting at a different rate for every 3 month model cycle based on the time elapsed. By convention in the UK, in line with the use of annual public sector budgets, discounting is applied annually considering the first 12-month period as

involving current costs and each subsequent 12-month period requiring discounting for an additional year's delay. In some models with differential extended survival and multiple future events, the choice of discounting method may have a large impact on the size of the ICERs generated by a model. However, using annual discounting in the company model for this appraisal has only a minor effect, since no claim is made for any survival gain, reducing the estimated long-term base case ICERs by £3 per QALY gained.

5.5.11 Parameter uncertainty

For PSA, the standard error of most parameters in the company model is set to 10% of the estimated mean. For estimated response rates these values are too small. The ERG has estimated that, based on trial data, the following proportions detailed in Table 24 are more accurate.

Table 24 ERG standard error estimates for response rate parameters

Response definition	Treatment arm	Standard error at 3 months	Standard error at 6 months
Post-hoc	Ikervis	20%	18%
Post-hoc	AT	39%	39%
Primary trial outcome	Ikervis	16%	12.5%
Primary trial outcome	AT	28%	19.5%

AT = artificial tears

The 10% ratio is also applied to the cost of operations from the NHS Schedule of Reference Costs, whereas the ERG has estimated that the appropriate ratio is between 4% and 4.5%. Applying these revised parameter values has the effect of reducing the estimated base case probabilistic ICER by about £25 per QALY.

5.5.12 Definitions of response

The company base case analysis is based on a post-hoc definition of response to treatment which is more restrictive than that specified in the SANSIKA trial protocol, requiring at least a 3 point improvement in CFS score, rather than the original 2 point reduction. This change has a large impact on outcome estimates and therefore on the estimated cost effectiveness of Ikervis. The reason for this large effect is displayed visually in Figure 6, which shows how the more restrictive definition excludes the level of benefit which most favours the vehicle treatment arm.

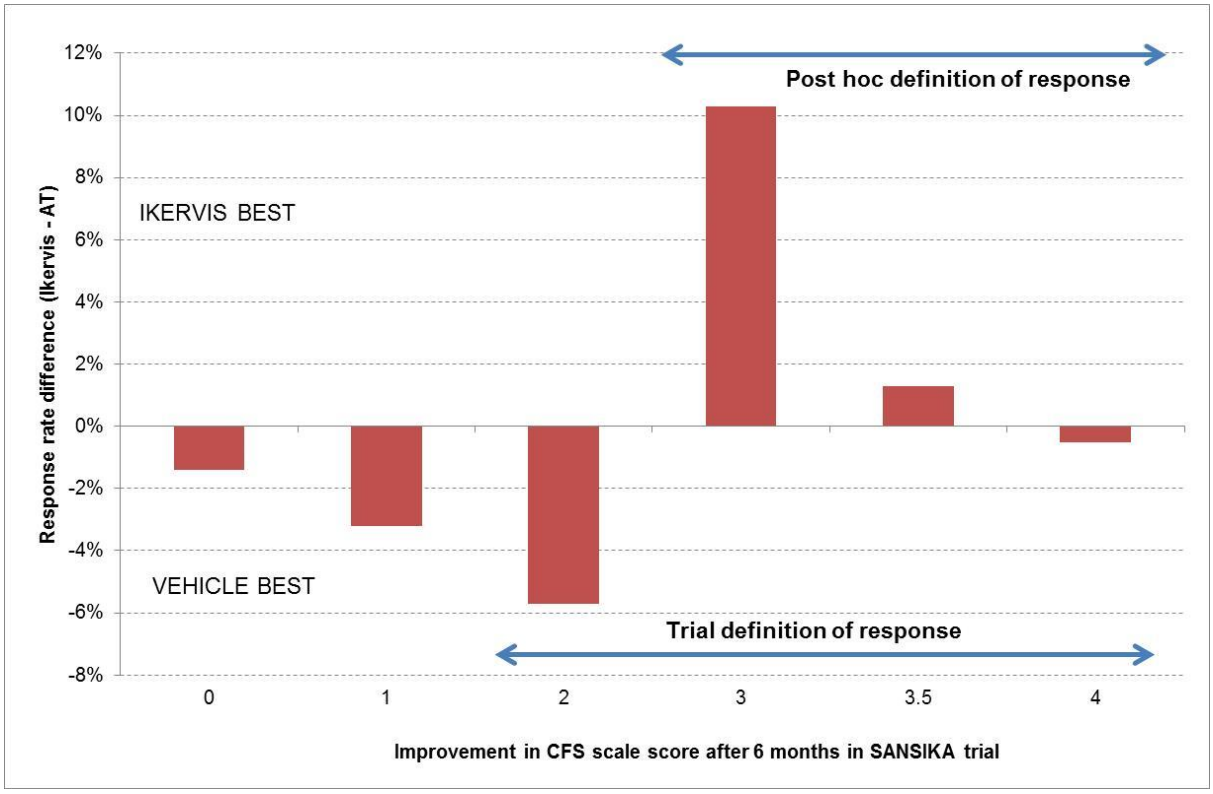

Figure 6 Comparison of the relative response rate difference (Ikervis – vehicle) across the range of possible CFS benefit experience by SANSIKA patient at 6 months

To exemplify the differences attributable to the choice of response definition, all results generated by the ERG from the amended model are displayed using both definitions.

5.6 Conclusions of the cost effectiveness section

It is the ERG's view that the most important issue to address is whether the effectiveness evidence available at the present time is adequate to allow a conventional cost effectiveness assessment to be made. Although it is arguable that the SANSIKA trial indicates some degree of benefit to patients compared to an alternative treatment not containing CsA as an active agent, the trial failed to achieve its pre-specified primary objective (superiority using the defined measure of response). Thus it may be that Ikervis will receive a marketing authorisation for offering on balance more benefit than harm. However, to carry out a full cost effectiveness comparison it is necessary to have a coherent chain of evidence by which to arrive at quantifiable estimates of relative effectiveness between Ikervis and currently available treatments to UK patients. Due to the choice of comparator in the key trial, no such chain of evidence exists. Therefore, the ERG concludes that the only viable alternative is a cost minimisation exercise assuming equivalent effectiveness.

The model submitted by the company is framed around evidence from the SANSIKA trial, but uses as base case a post-hoc alteration to the key outcome definition which substantially improves the estimated ICER in favour of Ikervis. The ERG has identified several problems with the implementation of the model, and the use made of SANSIKA results to populate the model. The ERG has sought to rectify errors and improve the calibration of key parameter values wherever possible. However, there is an important structural problem with the implementation of the Markov model design which is too far-reaching for the ERG to correct without rebuilding the two core sections of the model.

The ERG concludes that, even if the model were to be accepted as a basis for decision-making, implementation of the ERG amendments leads to the estimated base case ICER per QALY gained being considerably greater than that presented in the CS.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

This section shows the impact on the ICER per QALY gained of changes made by the ERG to the company model. Due to issues outline in section 5.5.1 relating to the lack of evidence to address the decision problem, the resultant figures should not be understood to be any expression of support for the validity of the model.

A detailed summary of the various model corrections and amendments identified and implemented by the ERG is shown in Table 15. This includes results for both definitions of response to treatment – the SANSIKA trial primary outcome measure (at least 2 point improvement on CFS scale and 30% improvement in OSDI), and the post-hoc measure (at least 3 point CFS improvement and 30% improvement in OSDI).

The two most influential ERG changes are the use of treatment discontinuation rates estimated directly from SANSIKA Kaplan-Meier results, and the use of differential utility values for treatment responders sourced from the SANSIKA trial results.

Of secondary importance to the estimation of the ICER are the correction of erroneous parameter values for AT use, and the revision of treatment costs to reflect monthly prescribing.

The possibility that the trial population includes some more recently diagnosed patients whose condition may be more amenable to non-CsA treatments cannot be resolved from the limited trial evidence currently available. If confirmatory evidence is obtained, then limiting CsA-based treatment to more established severe DED would result in better relative effectiveness for Ikervis, though the extent of effect on the estimated ICER cannot be estimated with any confidence.

The serious errors identified by the ERG in the coding of the core worksheets of the company model are disturbing. However, it is not possible to be sure of the extent and, in what direction, the cost effectiveness results would be altered by their correction.

Table 15 Cost effectiveness results for Ikervis versus vehicle with ERG revisions to company's base case comparison

Model scenarios & ERG revisions	Ikervis + AT		Vehicle + AT		Incremental		ICER	ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change
A. **Company's base case (Post-hoc response)**	**£15,997**	**9.744**	**£15,283**	**9.707**	**£713**	**0.037**	**£19,156**	-
R1. Age/sex modelling	£15,238	9.277	£14,533	9.241	£705	0.036	£19,382	**+ £226**
R2. Treatment discontinuation	£15,990	9.742	£15,245	9.713	£746	0.030	£25,020	**+ £5,864**
R3. Treatment costs	£16,181	9.744	£15,365	9.707	£816	0.037	£21,916	**+ £2,760**
R4. Responder utility	£15,997	9.763	£15,283	9.733	£713	0.029	£24,473	**+ £5,317**
R5. Artificial tears use	£16,526	9.744	£15,670	9.707	£856	0.037	£22,992	**+ £3,836**
R6. Discounting	£16,206	9.872	£15,483	9.834	£723	0.038	£19,153	**- £3**
B. Applying **R1-R6**	**£16,200**	**9.414**	**£15,273**	**9.397**	**£927**	**0.017**	**£53,253**	**+ £34,097**
C. **Alternative base case (SANSIKA response)**	**£16,132**	**9.788**	**£14,987**	**9.754**	**£1,145**	**0.034**	**£33,291**	**-**
R1. Age/sex modelling	£15,370	9.320	£14,244	9.287	£1,126	0.033	£33,625	**+ £334**
R2. Treatment discontinuation	£16,043	9.762	£14,987	9.754	£1,056	0.008	£133,290	**+ £99,999**
R3. Treatment costs	£16,293	9.788	£15,058	9.754	£1,235	0.034	£35,915	**+ £2,624**
R4. Responder utility	£16,132	9.754	£14,987	9.782	£1,145	-0.027	DOM	**-**
R5. Artificial tears use	£16,893	9.788	£15,658	9.754	£1,235	0.034	£35,916	**+ £2,625**
R6. Discounting	£16,343	9.916	£15,183	9.881	£1,160	0.035	£33,290	**£0**
D. Applying **R1-R6**	**£16,518**	**9.406**	**£15,236**	**9.458**	**£1,282**	**-0.052**	**DOM**	**-**

QALYs = quality adjusted life years; DOM = dominated (more costly and less effective)

7 DISCUSSION

Currently different formulations of CsA are used to treat patients with DED and severe keratitis which has not improved despite treatment with AT in clinical practice in England. These include Restasis (0.05% CsA drops), Optimmune (0.2% CsA ointment) as well as 2% CsA drops. Restasis is the only product with a licence for use to treat DED, albeit only in the US, not in Europe. Recently published systematic reviews[39,40] of CsA appear to confirm that various formulations of CsA (most commonly Restasis 0.05% which is typically administered twice a day) are safe but there is currently a lack of evidence for clinical efficacy from RCTs; this is commonly attributed to the heterogeneity of both DED and the populations included in studies to date.[39,40] Indeed, none of the RCTs included in two recent systematic reviews[39,40] had studied CsA in a wholly severe DED population. Expert advice to the ERG suggests, however, that ophthalmologists working in clinical practice in England consider that the formulations of CsA currently used are clinically effective.

In the current STA, the company has presented evidence for the clinical effectiveness of Ikervis (CsA 0.1% administered once daily) from the pivotal trial (SANSIKA) and supportive trial (SICCANOVE); patients in both trials were treated for 6 months with Ikervis. The comparator used in both of these trials is the Ikervis vehicle (albeit using different excipients). The use of vehicle as a comparator was stated by the company to be at the recommendation of the EMA CHMP. Vehicle is considered to be more than simply a placebo "since eye drop vehicles are known to have some beneficial effect on their own" (CS, page 27). Indeed, both trials reported an improvement over time for all clinical efficacy outcomes in the vehicle arms as well as the Ikervis arms. However this benefit may also be partially, or indeed solely, attributed to the concomitant use of AT in the vehicle arm (which may also have some benefit in the Ikervis arm).

It is, however, unclear whether the vehicle used in the SANSIKA trial should be considered similar to that used in the SICCANOVE trial, despite the company claiming the two excipients (CKC and BAK) are equivalent and citing the EMA CHMP as support for this view. The ERG notes that the rate of some AEs (eye irritation, eye pain, site irritation and site pain) differed between these trials and considers that this may be due to differences in the vehicle. Indeed, during the clarification process, the company confirmed that a smaller proportion of ocular severe events was observed with the CKC excipient (6.2%) used in SANSIKA than with the BAK excipient (27.5%) used in SICCANOVE.

Neither trial reported a statistically significant difference between groups at 6 months for their respective primary endpoints. Thus the relative superiority of Ikervis versus vehicle has not been demonstrated. In the SANSIKA trial the primary outcome was the composite CFS-OSDI responder rate whilst in the SICCANOVE trial the co-primary outcomes were change in CFS and change in OSDI. Since the SICCONOVE population included patients with moderate to severe DED, only the results of the post-hoc analyses of patients with severe DED were relevant to the decision problem and then only as exploratory outcomes.

A number of statistically significant findings between arms were reported for measures of signs in post-hoc subgroup analyses in SICCANOVE. Measures of the same outcomes that were also analysed in the severe DED population in SANSIKA were not, however, statistically significant, except for change in CFS. Only two pre-specified outcomes and three post-hoc analyses reported a statistically significant difference between arms in SANSIKA. Aside from the (more stringently defined) post-hoc CFS-OSDI response rate (CFS improvement ≥ 3 and OSDI improvement ≥ 30%), four of these outcomes reported on changes in signs (the pre-specified change in CFS and HLA-DR expressions on the conjunctival cell surface (AUF) and post-hoc CFS improvement of ≥ 3 points and worst tear film osmolality in patients with elevated tear film osmolarity at baseline). Inflammation is a core element of DED and so the significant decrease in the inflammatory marker (HLA-DR) in the Ikervis arm is encouraging and appears to demonstrate that Ikervis has an anti-inflammatory effect. No statistically significant differences in symptom measures were reported between arms in the SANSIKA trial or in patients with severe DED in SICCANOVE, whereas the rate of AEs was higher in the Ikervis arm compared to vehicle in both trials. AEs were mostly at the time of instillation and were mild to moderate and transitory in nature. It can therefore be concluded that the Ikervis safety profile is acceptable. No differences between treatment arms were reported in terms of HRQoL in SANSIKA, perhaps reflecting the lack of difference between arms in symptoms and a greater rate of AEs in the Ikervis arm. The lack of a difference between arms in HRQoL may also support the suggestion that the vehicle is possibly an efficacious intervention by itself. This also raises questions about the appropriateness of using vehicle as a proxy outcome for AT alone in the cost effectiveness analysis (as the company has done) since the vehicle appears to be having some effect over and above that which may be expected from AT alone. Furthermore, while AT is commonly used for treating DED, patients are often managed concurrently with a multitude of other agents including Omega fatty acids, tetracyclines (which were permitted in SANSIKA) and topical steroids (which were not permitted in SANSIKA).

The Ikervis vehicle (containing CKC or BAK) is not commercially available and therefore is not used in clinical practice. However, it is noted that the company has previously claimed that the Ikervis vehicle is of similar efficacy to Cationorm ocular lubricant, which it reports as having demonstrated a significant effect on signs and symptoms versus Vismed eye drops in the phase III NOSIKA RCT.[22] Cationorm is however not routinely used in England whereas off-label use of various CsA formulations to treat severe DED are used in England. Therefore the ERG considers that a comparison of Ikervis to alternative CsA formulations is the ideal comparison. Unfortunately, there is a lack of trial evidence to enable such a formal comparison to be made either directly or indirectly. A crude comparison of trials comparing Restasis to its vehicle and Ikervis to its vehicle was carried out by the ERG. It was noted that the improvement in the Ikervis trial arms as measured by change in signs (CFS) and symptoms (OSDI) compared favourably to the improvement in Restasis trial arms but the rate of AEs may be higher with Ikervis than Restasis. However, the results of these crude comparisons must be treated with extreme caution and considered only exploratory at best. In terms of other CsA formulations, the ERG notes that Ikervis may offer an added benefit for patients allergic or intolerant to lanolin, which is used as a vehicle for Optimmune (CsA 0.2%) ointment.

Regarding the primary outcome used in SANSIKA, while this is a composite endpoint using validated and recognised instruments for measuring signs (CFS) and symptoms (OSDI), the concept of a CFS-OSDI responder defined in such a manner is nevertheless an artificial one in clinical practice. Indeed, defining patients as a responder for CFS or OSDI has rarely been used in clinical studies (SICCANOVE being the first such study the ERG is aware of). Therefore, the clinical relevance of a CFS-OSDI responder may be questioned and, in particular, the different thresholds used to measure response (e.g. CFS improvement ≥ 2 rather than ≥ 3) appear arbitrary and not evidence-based. This is of particular importance when it is considered how the cost effectiveness results differ when using different definitions of CFS-OSDI response (discussed further below).

Another uncertainty relates to the apparent improvement in signs reported in SANSIKA as measured by CFS and HLA-DR (AUF) but not symptoms (as measured by OSDI or VAS) and the clinical significance of this. To some extent, this finding could be described as not unexpected, given the acknowledged lack of correlation between signs and symptoms.[1,2] It may therefore be speculated that the reason why the difference in signs does not translate to a difference in symptoms in the current trials is because such an effect may take longer than 6 months to occur.

In terms of the cost effectiveness results, one major problem with deriving any conclusions again lies with the lack of any comparison with other CsA formulations. As such, the ERG considers that only a cost minimisation analysis comparing Ikervis to Restasis and two alternative unlicensed CsA formulations (CsA 2% eye drops and Optimmune 0.2% ointment) is possible. However, this requires an assumption that the treatments being considered are of equivalent efficacy, are associated with similar AEs and incur similar administration, prescribing and monitoring costs. As noted above, such assumptions cannot be robustly supported or refuted.

A second major problem with the cost effectiveness analysis is that the company's model has a number of major structural flaws. This means that the ERG does not trust the company's cost effectiveness results comparing Ikervis plus AT versus AT to be valid or reliable. Nevertheless, the ERG has attempted to address key issues where possible. By doing so, the ERG estimates that the ICER is higher than £50,000 per QALY gained when response to treatment is based on a post-hoc composite endpoint (CFS improvement ≥ 3 and OSDI improvement ≥ 30%) as opposed to the company's estimate of £19,156. When the composite endpoint that was the pre-specified primary outcome for SANSIKA is used (CFS improvement ≥ 2 and OSDI improvement ≥ 30%), the ERG shows that Ikervis plus AT is dominated by AT (whereas the company's ICER is £33,291 per QALY gained). However, the important structural problem with implementation of the model design is too far-reaching for the ERG to correct without rebuilding core sections of the model. Extreme caution must therefore be taken when attempting to interpret the company's and ERG's cost effectiveness results.

8 OVERALL CONCLUSIONS

The ERG draws the following conclusions:

- Clinical evidence from the pivotal SANSIKA trial does not demonstrate significant differences between Ikervis and vehicle for the majority of outcomes measured, including the primary outcome measured in this trial, despite such differences being apparent in the results of the post-hoc analyses of patients with severe DED in the supportive SICCANOVE trial. Improvements over time were however observed for the majority of outcomes in both trial arms in both trials. Only a minority of patients who received Ikervis reported treatment-related AEs and the safety profile is therefore acceptable.
- A comparison of Ikervis with other CsA formulations is more appropriate for evaluating both clinical and cost effectiveness than a comparison with vehicle (or, by proxy, AT) since vehicle is not used, or commercially available, for treating severe DED in clinical practice in England.
- However, a current lack of (direct or indirect) clinical evidence precludes a reliable, or robust, clinical comparison of Ikervis with any the other CsA formulations currently in use (off-label) in clinical practice in England.
- Clinical efficacy from the pivotal SANSIKA trial utilises CFS-OSDI response as the primary outcome in which response is defined as an improvement of CFS ≥ 2 and OSDI ≥ 30%. A post-hoc analysis is utilised for the company's base case economic model in which response is defined as CFS ≥ 3 and OSDI ≥ 30%. While changes in CFS and OSDI are considered valid outcomes for measuring signs and symptoms associated with DED, the ERG is unaware of evidence to support the use of a composite CFS-OSDI endpoint as a robust and reliable measure of efficacy (regardless of the threshold used for CFS improvement).
- Using the post-hoc analysis of CFS-OSDI response from the SANSIKA trial the company's economic base case generates an ICER per QALY gain of £19,156 for Ikervis plus AT versus AT; however, using the SANSIKA trial pre-specified primary outcome results in an ICER per QALY gained of £33,291 for Ikervis plus AT versus AT.
- Six ERG amendments to the model utilising preferred alternative parameter values result in an ICER per QALY gained of £53,253 for Ikervis plus AT versus vehicle plus AT using the post-hoc definition of CFS-OSDI response, whereas Ikervis plus AT is dominated by vehicle plus AT (leads to fewer QALY gains and is more costly) when using the pre-specified primary outcome for the SANSIKA trial.
- Given the lack of (direct or indirect) clinical evidence for Ikervis compared with other CsA formulations, and given problems with the reliability of the company's cost effectiveness analyses, the ERG advocates a cost minimisation analysis for comparing Ikervis with other CsA formulations. This assumes equivalent clinical effectiveness of all CsA formulations and shows Ikervis to be less costly than Restasis but more costly than the two other CsA formulations currently in use in clinical practice (Optimmune 0.2% [ointment] and 2% CsA drops).

8.1 Implications for research

A direct comparison of Ikervis to other formulations of CsA would considerably improve the evidence base for both clinical and cost effectiveness. Ideally, this comparison should be made from an RCT that considers signs, symptoms, AEs and HRQoL as endpoints.

Trials with a comparator arm featuring AT alone (i.e. without a CsA vehicle) could enable an indirect treatment comparison of alternative CsA formulations, assuming homogeneous trial populations in terms of disease severity and other key characteristics.

Further research is required to determine the relevance of the composite CFS-OSDI endpoint. Assuming a composite endpoint of these two measures is considered relevant, additional research would be required to determine the threshold values for CFS and OSDI that should be used to define response.

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10 APPENDICES

10.1 Appendix 1: LRiG search strategies

The ERG completed a comprehensive search on 22nd December 2014 of the following databases:

- MEDLINE and MEDLINE In-Process (OvidSP)
- EMBASE (OvidSP)
- Science Citation Index (ISI Web of Science)
- Conference Proceedings Citation Index – Science (ISI Web of Science)
- Cochrane Library (Wiley Interscience):
    - Cochrane Database of Systematic Reviews
    - Cochrane Central Register of Controlled Trials
    - Database of Abstracts of Reviews of Effects (DARE)
    - Health Technology Assessment Database (HTA)

The databases were searched from inception to current date.

PubMed was also searched on 2nd February 2015 and limited to the last 6 months.

The following grey literature websites were also searched on 4th February 2015:

- European Medicines Agency (www.ema.europa.eu/)
- US Food and Drug Administration (www.fda.gov/)
- metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct/)
- Clinicaltrials.gov (www.clinicaltrials.gov)
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database (http://public.ukcrn.org.uk/search/)
- International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/)
- EU Clinical Trials register (https://www.clinicaltrialsregister.eu/)

The search strategies used by the ERG included MeSH and free text for the drug and condition. Filters for RCT, economic and systematic reviews were also included as appropriate.

10.2 Appendix 2: Additional data on adverse events

10.2.1 AEs reported only in SANSIKA

A detailed breakdown AEs for SANSIKA is presented in Table 25.

Table 25 Overview of treatment emergent AEs in SANSIKA

Type of AE	Ikervis (n = 154)		Vehicle (n = 90)	
	n (%) patients	n events	n (%) patients	n events
Any AE				
Part 1	88 (57.1)	175	42 (46.7)	88
Part 2*	113 (73.4)	275	N/A*	N/A*
Any treatment-related AE				
Part 1	57 (37.0)	95	19 (21.1)	30
Part 2*	70 (45.5)	128	N/A*	N/A*
Any ocular AE				
Part 1	66 (42.9)	112	27 (30.0)	44
Part 2*	86 (55.8)	160	N/A*	N/A*
Any treatment-related ocular AEs				
Part 1	57 (37.0)	90	18 (20.0)	29
Part 2*	70 (45.5)	118	N/A*	N/A*
Any AE leading to discontinuation †				
Part 1	21 (13.6)	34	9 (10.0)	11
Part 2*	31 (20.1)	51	N/A*	N/A*
Any ocular AE leading to discontinuation				
Part 1	18 (11.7)	29	6 (6.7)	8
Part 2*	27 (17.5)	40	N/A*	N/A*
Any severe ocular AE				
Part 1	9 (5.8)	16	5 (5.6)	8
Part 2*	11 (7.1)	19	N/A*	N/A*
Any SAE §				
Part 1	6 (3.9)	6	6 (6.7)	6
Part 2*	14 (9.1)	14	N/A*	N/A*
Any treatment-related SAEs				
Part 1	0 (0.0)	0	1 (1.1)	1
Part 2*	0 (0.0)	0	N/A*	N/A*
Any ocular SAE				
Part 1	0 (0.0)	0	1 (1.1)	1
Part 2*	0 (0.0)	0	N/A*	N/A*
Deaths				
Part 1	0 (0.0)	0	0 (0.0)	0
Part 2*	0 (0.0)	0	N/A*	N/A*

* Part 2 is for patients who received Ikervis for 12 months only, not those who received vehicle only for the first 6 months

† This category is about TEAEs that led to permanent discontinuation of treatment. All patients who stopped treatment were also discontinued from the study, except 1 patient in SANSIKA who continued the study and completed part 1

§ There was 1 SAE that started during Part 1 but its seriousness (i.e. event requiring hospitalisation) was known by the Investigators after Part 1 database lock

Source: Tables 53 and 55 of SANSIKA CSR

10.2.2 Types of AEs

A greater number of patients treated with Ikervis experienced ocular AEs than systemic AEs. From pooled data reported in the draft EPAR,[35] ocular AEs were reported by 42.7% of patients in the Ikervis arm and 27.6% in the vehicle arm as opposed to 24.5% and 28.2% systemic AEs in the Ikervis and vehicle arms respectively.

AEs that were reported to be statistically significantly higher in the Ikervis arm compared to the vehicle arm from the pooled analysis reported in the CS were:

- Instillation site pain: 50 (12.6%) versus 9 (2.6%), relative risk (RR) 4.77 (95% confidence interval [CI] 2.38 to 9.56)
- Eye irritation: 43 (10.9%) versus 10 (2.9%), RR 3.69 (95% CI 1.88 to 7.23)
- Instillation site irritation: 20 (5.1%) versus 4 (1.2%), RR 4.29 (95% CI 1.48 to 12.44)

Other AEs occurring in ≥ 2% of patients in any treatment arm from the pooled analysis were:

- Eye pain: 18 (4.5%) versus 13 (3.8%), RR 1.19 (95% CI 0.59 to 2.39)
- Meibomianitis 14 (3.5%) versus 12 (3.5%), RR 1.00 (95% CI 0.47 to 2.14)
- Lacrimal disorder 13 (3.3%) versus 10 (2.9%), RR 1.12 (95% CI 0.50 to 2.51)
- Conjunctival hyperaemia 11 (2.8%) versus 4 (1.2%), RR 2.36 (95% CI 0.76 to 7.35)
- Erythema of eyelid 10 (2.5%) versus 7 (2.1%), RR 1.23 (95% CI 0.47 to 3.19)
- Lacrimation increased 10 (2.5%) versus 2 (0.6%), RR 4.29 (95% CI 0.95 to 19.46)
- Visual acuity reduced 9 (2.3%) versus 12 (3.5%), RR 0.64 (95% CI 0.27 to 1.51)
- Ocular hyperaemia 8 (2.0%) versus 6 (1.8%), RR 1.14 (95% CI 0.40 to 3.27)
- Instillation site erythema 8 (2.0%) versus 0 (0%), RR 14.60 (95% CI 0.85 to 251.96)
- Hypertension 4 (1.0%) versus 11 (3.2%), RR 0.31 (95% CI 0.10 to 0.97)
- Blood pressure systolic increased 3 (0.8%) versus 8 (2.4%), RR 0.32 (95% CI 0.09 to 1.20)
- Influenza 2 (0.5%) versus 7 (2.1%), RR 0.25 (95% CI 0.05 to 1.17)

10.2.3 Treatment-related AEs

Overall, the draft EPAR[35] reports 55.8% patients who received Ikervis and 47.4% who received vehicle experienced at least one AE. Treatment-related AEs were reported by 35.9% patients in the Ikervis arm and 20.3% in the vehicle arm. A greater proportion of patients in the Ikervis arm experienced a severe treatment-related AE (21.7%) than in the

vehicle arm (10.3%). Treatment-related ocular AEs were also more common (35.1% versus 17.6%) than treatment-related systemic AEs (3.5% versus 4.4%).

10.2.4 AE severity and treatment discontinuation

From pooled data presented in the draft EPAR, discontinuation rates due to an AE or treatment-related AE were slightly lower in the pooled population than reported only in the SANSIKA trial: 12.1% and 9.3% respectively in the Ikervis arm versus 10.3% and 6.8% respectively in the vehicle arm. Most AEs giving rise to discontinuation were reported in the draft EPAR to be ocular AEs (instillation site pain, eye irritation, conjunctival hyperaemia).

10.2.5 Serious AEs and deaths

Pooled SAEs reported in the draft EPAR were relatively infrequent and were evenly distributed across the trial arms (3.8% in Ikervis and 4.7% in vehicle). One patient in each arm (0.3%) was reported to have experienced a treatment-related SAE in the CS. These were both ocular SAEs and reported in the vehicle arm of SANSIKA and Ikervis arm in SICCANOVE. There were no deaths reported in either arm in either trial.

10.2.6 Vital signs

The CS reports that vital signs (blood pressure, pulse rate and respiratory rate) showed no clinically significant change over time or between treatment groups in either SANSIKA or SICCANOVE. In addition, there was no evidence of a risk of systemic absorption (e.g. through the nasal mucosa) of ciclosporin. The draft EPAR further highlights there were few cases of ocular infections which had been reported in phase II studies. This report also noted that ciclosporin is known to have a carcinogenic potential and hence peri-ocular skin cancer and conjunctival or corneal neoplasia was included in the RMP [risk management plan] as an important potential risk although this risk is considered to be low at the specified dose for Ikervis. Finally, the risk for drug-drug interactions with Ikervis was considered to be likely to be low.

10.3 Appendix 3: Implementation of ERG decision model amendments

Model amendments implemented by the ERG are activated by a series of modification logic switches; these take the value 0 when the original model logic is active, and positive integer values (1, 2,…,n) when alternative values or assumptions are active. The logic switches are labelled Mod_1 to Mod_7 (Mod_3 was exploratory but is not used by ERG as it has no impact on any model ICERs, and is not described here).

1. USE ANNUAL DISCOUNTING INSTEAD OF CONTINUOUS DISCOUNTING (Mod_1)

Create range name Mod_1 (binary integer variable taking values 0 or 1)

On Sheets 'Ikervis Trace' and 'Artificial Tears Trace'

Enter formula in cell E10 as follows:

= INT(C10/12)

Copy formula in cell E10 to range (E11:E130)

Amend formula in cell AD11 as follows:

= AC11*(1/(1 + c.DiscRate)^IF(Mod_1 = 0,D11,E11))

Copy formula in cell AD11 to range (AD12:AD130)

Amend formula in cell AM11 as follows:

= AL11*(1/(1 + u.DiscRate)^IF(Mod_1 = 0,D11,E11))*AN11

Copy formula in cell AM11 to range (AM12:AM130)

2. USE ALTERNATIVE TREATMENT DISCONTINUATION RATES (Mod_2)

Create range name Mod_2 (integer variable taking values 0, 1 or 2)

On Sheet 'Transition Matrix'

Enter values in cells as follows:

Cell F37 = 0.162

Cell F38 = 0.122

Cell AF42 = 0.0589490

Cell AF43 = 0.0461775

Enter formulae in cells as follows:

Cell G35 = IF(Mod_2 = 0, D35/C35, 0.162)

Cell G36 = IF(Mod_2 = 0, D36/C36, 0.122)

Cell AC42 = IF(Mod_2 = 2, AF42, 1-EXP(-AB42 * 3))

Cell AC43 = IF(Mod_2 = 2, AF43, 1-EXP(-AB43 * 3))

3. USE SEPARATE AT USE RATES IN TRIAL ARMS & CORRECT PARAMETER VALUE ERRORS (Mod_4)

Create range name Mod_4 (binary integer variable taking values 0 or 1)

On Sheet 'Cost and resource use'

Enter formulae in cells as follows:

Cell D38 = IF(Mod_4 = 0, 14.89, 16.54)

Cell D39 = IF(Mod_4 = 0, 14.89, 13.24)

Cell C38 = IF(Mod_4 = 0, 7.32, 14.64)

Cell C39 = IF(Mod_4 = 0, 6.34.12.68)

4. USE STANDARD ERROS FROM DATA SOURCES FOR PSA (Mod_5)

Create range name Mod_5 (binary integer variable taking values 0 or 1)

On Sheet 'Cost and resource use'

Enter formulae in cells as follows:

Cell Z18 = 0.0395

Cell Z19 = 0.0446

Cell Z20 = Z21

Cell Z21 = ((Z18*AA18) + (Z19*AA19))/(AA18 + AA19)

Cell AB18 = IF(Mod_5 = 0,AA18/10,AA18*Z18)

Copy formula in Cell AB18 to Range AB19:AB21

On Sheet 'Transition Matrix'

Enter formulae in cells as follows:

Cell AB23 = IF(Mod_5 = 0,AA23/10,AA23*0.2)

Cell AB24 = IF(Mod_5 = 0,AA24/10,AA24*0.18)

Cell AB25 = IF(Mod_5 = 0,AA25/10,AA25*0.39)

Cell AB26 = IF(Mod_5 = 0,AA26/10,AA26*0.39)

5. USE STANDARD ERROS FROM DATA SOURCES FOR PSA (Mod_6)

Create range name Mod_6 (binary integer variable taking values 0 or 1)

On Sheet 'Ikervis Trace'

Enter formulae in cells as follows:

Cell S11 = S$3*CycleLength*IF(Mod_6 = 0,F11,(2*F10 + F11)/3)*AN11

Cell T12 = T$3*CycleLength*IF(Mod_6 = 0,G12,(2*F11 + G12)/3)*AN12

Cell U13 = U$3*CycleLength*IF(Mod_6 = 0,H13,(2*G12 + H13)/3)*AN13

Cell U14 = U$3*CycleLength*IF(Mod_6 = 0,AVERAGE(H13:H14), (2*H13 + H14)/3) *AN14

Copy formula in Cell U14 to Range U15:U130

On Sheet 'Artificial Tears Trace'

Enter formulae in cells as follows:

Cell V11 = V$3*CycleLength*IF(Mod_6 = 0,I11,(2*I10 + I11)/3)*AN11

Cell W12 = W$3*CycleLength*IF(Mod_6 = 0,J12,(2*I11 + J12)/3)*AN12

Cell X13 = X$3*CycleLength*IF(Mod_6 = 0,K13,(2*J12 + K13)/3)*AN13

Cell X14 = X$3*CycleLength*IF(Mod_6 = 0,AVERAGE(K13:K14),(2*K13 + K14)/3)*AN14

Copy formula in Cell X14 to Range X15:X130

6. USE TREATMENT SPECIFIC RESPONSE-RELATED UTILITY VALUES (Mod_7)

Create range name Mod_7 (binary integer variable taking values 0 or 1)

On Sheet 'Utilities'

Create a table of utility values as follows:

Cell M10 = u.NoResponse Copy Cell M10 to Range N10:P10
Cell M11 = 0.055
Cell N11 = 0.104
Cell O11 = 0.097
Cell P11 = 0.135
Cell M9 = M10 + M11 Copy Cell M9 to Range N9:P9

On Sheet 'Ikervis Trace'

Enter formulae in cells as follows:

Cell AL11 = (AI11*IF(Mod_7 = 0,u.Response,IF(posthoc = 0,Utilities!$M$9,Utilities!$O$9)) + AJ11*u.NoResponse)*(CycleLength/12)

Copy formula in Cell AL11 to Range AL12:AL130

On Sheet 'Artificial Tears Trace'

Enter formulae in cells as follows:

Cell AL11 = = (AI11*IF(Mod_7 = 0,u.Response,IF(posthoc = 0,Utilities!$N$9,Utilities!$P$9)) + AJ11*u.NoResponse)*(CycleLength/12)

Copy formula in Cell AL11 to Range AL12:AL130

7. AGE/SEX/EVENT POPULATION WEIGHTED AVERAGE RESULTS

This modification to the company model requires use of a new VBA macro **GetICER** (activated by pressing **Ctrl + Shift + I**). The calculations are carried out in a new worksheet (ByAge) which is included in the ERG modified version of the model, together with the new macro code.

On Sheet 'Inputs',

Enter formulae in cells as follows:

Cell W4 = ByAge!A2
Cell W5 – ByAge!B2

On Sheet 'Mortality',

Enter formulae in cells as follows:

Cell F11 = C11*MalePropn + D11*(1-MalePropn)

Copy formula in Cell F11 to Range F12:F111