NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Ciclosporin for the Treatment of Severe Keratitis in Adult Patients with Dry Eye Disease that has Not Improved Despite Treatment with Tear Substitutes

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Single technology appraisal (STA)

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Executive summary

The approved name of the proposed technology is ciclosporin, the brand name is Ikervis® (section 1.1). European Marketing Authorization Application for Ikervis was filed with the European Medicines Agency on 6th December 2013, and expected approval is the middle of April 2015. The proposed indication for Ikervis in the UK is the treatment of severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes. Ikervis is contraindicated for patients who present with hypersensitivity to CsA or to any of its excipients, and for patients with active or suspected ocular or peri-ocular infection.

Dry eye disease (DED) (keratoconjunctivitis sicca) is a multifactorial, chronic and progressive ophthalmic disease causing inflammation and damage to the ocular surface with increased osmolarity of the tear film (1, 2). Symptoms of DED include discomfort, visual morbidity or disturbance and tear film instability with potential damage to the ocular surface (1, 3). The symptoms of DED usually correlate poorly with the objective clinical findings (4-7).

Complications associated with DED include conjunctivitis, corneal ulceration, and corneal infection (8). DED may also compromise results of corneal, cataract or refractive surgery (9).

Once DED has developed, inflammation becomes the key mechanism of injury to the entire ocular surface (the adnexa, conjunctiva and cornea) (5, 10, 11). 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 (12). Treatment may also avoid the negative impact on functional visual acuity, resulting in impaired vision, ocular fatigue, and inability to read or drive (13, 14).

Currently available medical options include artificial tear products, lubricants, topical steroids and ciclosporin A (CsA) (section 2.6). Artificial tears aim to alleviate mild to moderate symptoms by replacing or retaining moisture on the ocular surface, providing only short-term relief at best, and requiring frequent

dosing throughout the day. The preservative in many artificial tear products often causes eye irritation due to the use of benzalkonium chloride (BAK) and its epithelial toxic effects. The NHS Prescribing Guidelines For Dry Eye Syndrome (2013) (8) clearly state the need for a preservative-free formulation for patients with severe dry eye with ocular surface disease and impairment of lacrimal gland secretion. Lubricants are classified as ‘health products’, proof of their efficacy is not required by Health Authorities (15), and many are available over-the-counter. Any potential for symptomatic improvement provided by topical steroids should be considered alongside their known iatrogenic ocular side effects including glaucoma and cataract (11, 16-19), with severe intraocular pressure (IOP) increases which may require surgery (20). Due to the well known likelihood of complications all patients taking topical corticosteroids in the long-term require regular monitoring of IOP and cataract formation (21). 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 efficacy has not been clearly demonstrated.

Ikervis is a sterile, positively charged, oil-in water, unpreserved ophthalmic emulsion that contains the active ingredient ciclosporin (CsA) Ph Eur. at a concentration of 1 mg/ml (0.1% w/w). Ikervis is packaged in 30 and 90 single-dose containers. Based on current evidence, the average duration of treatment for DED is anticipated to range from 20 weeks to 52 weeks (22).

CsA has an anti-inflammatory effect on the cornea and the lacrimal (tear) gland (23) thereby reducing inflammation in the eye (section 1.2). This is important because dry eye is an inflammatory ocular disease evidenced by the inflammatory changes that occur on the entire ocular surface (1, 10, 11). Following topical ocular administration, CsA enters corneal and conjunctival infiltrated T-cells and subsequently blocks the expression of anti-inflammatory cytokines (24). The topical delivery of Ikervis is optimised by cetalkonium chloride (CKC) that acts as a cationic agent to deliver a cationic charge that

plays an important role in both the stability of the emulsion and biological performances of Ikervis through ocular absorption of CsA, without acting as a preservative agent. The emulsion formulation is specifically designed to prolong the residence time of each eye drop on the epithelial layer of the eye (25).

In the absence of an approved and valid active comparator, the Ikervis excipient “Vehicle” was used as a comparator in the clinical trial programme, as recommended by the European Medicines Agency (EMA), and because eye drop vehicles are known to have some beneficial effect on their own (section 2.7). However, in the economic evaluation, Ikervis plus artificial tear substitutes was compared to artificial tear substitutes alone (i.e. standard care).

The clinical evidence in this submission comes from two phase III, multicentre, randomized, vehicle-controlled, double-masked trials of Ikervis (ciclosporin 0.1%), SICCANOVE (NVG06C103) and SANSIKA (NVG10E117) (section 6.3). SANSIKA was performed in DED patients with severe keratitis, while SICCANOVE included DED patients with moderate to severe keratitis (17% at baseline had severe keratitis). The duration of treatment was 12 months in SANSIKA; efficacy was assessed up to six months, and an additional six months of open label treatment was incorporated to assess safety. The duration of treatment was six months in SICCANOVE. It’s important to note that the Ikervis formulation is different in SICCANOVE and SANSIKA. In SICCANOVE, the excipient was benzalkonium chloride (BAK); in SANSIKA, the formulation contained CKC. In both formulations, these excipients were used as a cationic agent rather than a preservative agent.

The co-primary efficacy endpoints in SICCANOVE are change from baseline in corneal fluorescein staining (CFS) (using the modified Oxford Scale) at month six, and change from baseline in the symptoms Global Score (using a visual analogic scale) at month six. In SANSIKA, the composite primary efficacy outcome assessed responders, defined as patients with an improvement of ≥2 points from baseline in CFS and an improvement by ≥30% from baseline in symptoms (using the Ocular Surface Disease index OSDI)

after 6 months of treatment (CFS-OSDI responder rate). CFS is an objective measure of ciclosporin's effect.The OSDI assesses ocular discomfort according to symptoms.

In SICCANOVE, the between groups difference in change in CFS from baseline (-0.22; 95% CI: -0.39, -0.06) was statistically significant (p=0.009) at six months in favour of the Ikervis group (section 6.5). The improvement in this objective endpoint indicates a therapeutic benefit in comparison to treatment with the vehicle. These results were supported by a non-parametric analysis. It should also be noted that the results of these post-hoc analyses showed that the efficacy of Ikervis was greater in the most severe cases (grade 4 on the modified Oxford scale) than in the overall study population.

Findings from secondary analyses indicate that the improvement in the objective sign of CFS is present as early as 1 month and also after 3 months of treatment. For the Global VAS score, the estimated between groups difference (-0.39; 95% CI: -3.54, 2.76) was not statistically significant (p=0.808), therefore the second primary objective was not met. However, the percentage of responders (predefined as a percentage decrease from baseline of at least 25% in Global VAS score) at Day 168 (50.21% vs. 41.94%) was statistically significantly different between treatment groups in favour of Ikervis (p=0.048).

Therefore, even though the estimated mean difference in Global VAS score between the treatment groups was small, almost 10% more in the Ikervis group responded.

For SANSIKA, CFS-OSDI responder rate (the composite primary endpoint) at month six was slightly higher (improved) (+5.5 points) in the Ikervis group (44 patients, 28.6%) than in the vehicle group (21 patients, 23.1%); however, it was not statistically significant. Analysis of the CFS-OSDI responder rates in the open-label study (where all patients received Ikervis) were similar in both treatment groups at Months 9 and 12. Between Month 9 and Month 12, in the Ikervis/Ikervis group it increased by 5.5 points from 33.6% to 39.1% compared with 2.6 points in the vehicle/Ikervis group, from 35.4% to 38.0%.

After a marked increase in CFS-OSDI responder rate during the first 6 months with Ikervis, for patients who received Ikervis for an additional six months, the rate increased further but less rapidly. In the vehicle group, the CFS-OSDI responder rate increased during the first 6 months (24.4% at Month 6), and increased rapidly when patients treated with vehicle switched to Ikervis for the open label study (38.0% at Month 12).

When CFS was analysed as a secondary endpoint in SANSIKA, a significant improvement of corneal staining over time was reported at Month 6 (p= 0.037), and as early as Month 3 (p=0.024). These findings were supported by a non-parametric analysis. The difference at six months represents a ratio of 1.50 in the damaged surface area, meaning 50% more dots on average in the vehicle group than in the Ikervis group, a clinically relevant outcome at the population level for the treatment of keratitis (section 6.7).

Other ways to represent the clinical relevance of the effect on CFS are to calculate the odds ratio and the excess rate of patients reaching at least a given minimal improvement when comparing Ikervis and vehicle groups. In SANSIKA, the odds ratio to obtain a large gain in CFS (at least 1 grade, but also 2 grades, etc.) varied from 1.67 at Month 1 (not statistically significant) to 1.96 (p=0.026) at Month 6, considered to be clinically relevant. The excess rate for gaining more than two grades was 20.8% (p=0.002) in patients treated with Ikervis for three months, and for gaining more than 3 grades it was 21.2% (p=0.001) in patients treated for six months. These percentages translate into numbers needed to treat (NNTs) of 4.8 and 4.7, respectively, which is considered to be clinically relevant.

Both Ikervis and Vehicle markedly improved symptoms, assessed using the OSDI.

The incidence of ocular adverse events (AEs) was higher in the Ikervis group than the vehicle group in SICCANOVE (42.6% vs. 26.8%) and in SANSIKA (37.0% vs. 20.0%); most were mild to moderate in severity. The most common treatment-related AEs included eye irritation, eye pain and instillation site pain which were usually transitory and occurred during instillation.

IN SICCANOVE, a total of 22 serious AEs were reported during the study with one event being related to treatment. This AE (corneal decompensation) consisted of severe epithelial erosion of the cornea which resolved without sequelae.

in SANSIKA, there were 22 SAEs of which only one (ocular) was considered by the Investigator to be definitely related to the study drug (a severely reduced visual acuity in 1 patient treated with vehicle).

Over 12 months in SANSIKA, treatment with Ikervis was discontinued due to treatment-related AEs in 20.1% of patients. A negligible systemic passage of Ikervis has been shown in both SICCANOVE and SANSIKA.

Vitals signs (blood pressure, pulse rate and respiratory rate) showed no clinically significant change during either study and there were no differences between treatment groups.

The *de novo* economic evaluation, a cost utility analysis, utilises a Markov framework to assess the cost-effectiveness of Ikervis compared to the standard of care (artificial tear substitutes) in adult patients with DED and severe keratitis whose disease had not adequately responded to tear substitutes. A 30 year time horizon was considered sufficiently long to reflect differences in costs and health effects (QALYs) between treatment groups. The perspective considered was that of the NHS/PSS, and both costs and health benefits were discounted at 3.5%, all in accordance with the NICE reference case. The model is based, where possible on information from SANSIKA. Where information was not available from this study, it was informed by publically available information including other randomised studies identified via a formal systematic review and from national databases. Full and extensive sensitivity analyses were also conducted. As such, the modelling approach used synthesises all available information in a single, robust framework.

The model captures three health states; response (an OSDI improvement from baseline of ≥30% and a CFS improvement from baseline ≥3), non-response and death. Responders have a higher quality of life than non-

responders. Utilities are derived from data extracted from the SANSIKA trial and are used to capture the incremental HRQoL/utility benefit to patients of responding to treatment.

A number of assumptions in the model are considered pivotal. It was assumed that DED and its treatments impose no additional mortality risk compared with the general population, and, given the lack of long-term data and the fact that there is no contradictory evidence, transition probabilities remained constant over time. We also assumed that treatment-related AEs do not have a significant effect on quality of life, AE treatment costs are low and that incidence rates in routine practice will be low. While these assumptions were not formally modelled, they are implicit in the treatment specific discontinuation rates.

Similarly, quality of life is kept constant over time, conditional on response status. As reflected in the SANSIKA trial design and its expected license, patients are assumed to have one drop of Ikervis per eye per day. In SANSIKA, it was reported that 97.6% of patients had a diagnosis of DED in both eyes. To reflect clinical practice in the UK, the treatments selected to represent the comparator, polyvinyl alcohol, carbomers and paraffin, are also used as background therapy in the model. Management with permanent punctal occlusion is 100% efficacious. This rate is justified as patients are modeled to only receive permanent plugs if they were responsive to temporary plugs. While this likely overestimates the benefit of permanent punctal occlusion, it is assumed for simplicity due to the very small number of patients expected to receive this treatment. We also assume that patients responsive to punctal occlusion have the same utility gain as those responsive to Ikervis/vehicle. The model uses constant transition probabilities (excluding death) as there is no evidence to suggest that they should vary as a patient ages. As all therapies are self-administered, there are no administration, monitoring and testing costs incurred.

The base case analysis shows that, compared to artificial tears (AT) alone, Ikervis results in an incremental lifetime cost to the UK NHS of £713 per

patient (£15,997 minus £15,283) but offers an additional 0.04 QALYs (9.74 minus 9.71). The ICER is therefore £19,156 per QALY gained.

Table A1 Base-case cost-effectiveness results (deterministic model)

	Ikervis	**Artificial tears alone**
Trial costs	£662	£266
Maintenance costs	£1,080	£160
Temporary punctal occlusion costs	£358	£367
Permanent punctal occlusion costs	£35	£36
Non-responder costs	£21,406	£21,941
Total costs (undiscounted)	£23,542	£22,770
Total costs (discounted)	£15,966	£15,283
Difference in total costs	£713	N/A
LYG	N/A	N/A
LYG difference	N/A	N/A
QALYs	9.74	9.71
QALY difference	0.037	
ICER	£19,156	

The parameter that has the greatest impact on the ICER in univariate deterministic sensitivity analysis is the absolute utility value for a treatment responder (however defined). The responder utility that would be required to result in Ikervis being cost-effective at a threshold of £30,000 per QALY gained is approximately 0.05, a smaller value than that observed in both SANSIKA and the published literature. (26) (27) When the absolute utilities in Schiffman 2003 (26) (0.78 for responders and 0.72 for non-responders) were used in the model, the incremental lifetime costs remain unchanged but the incremental lifetime QALY gain decreases from 0.037 to 0.029. This change results in the ICER increasing to approximately £24,800 per QALY gained. However, it should be noted that these utility values were generated using a TTO based approach.

The following parameter altered in the sensitivity analysis had only a marginal effect on the base care ICER: using a three month rather than a six month treatment duration for Ikervis, shortened the time horizon, and each patient receives Ikervis treatment for one eye rather, and was robust to all other parameter changes.

Probabilistic sensitivity analysis confirms that Ikervis produces a benefit to patients, generating a utility gain compared with artificial tears in all 1000 simulations. At a cost-effectiveness threshold of £20,000 per QALY gained, Ikervis is cost-effective in approximately 46% of simulations. This increases to 71% at £30,000 per QALY. The probabilistic ICER of Ikervis is £18,835 per QALY gained.

In summary, there is robust evidence from two well-designed clinical trials of Ikervis efficacy on keratitis compared to vehicle at 6 months. In both studies, symptoms markedly improved over time in both groups. These results demonstrate the improvement in the objective endpoint CFS with Ikervis, indicating a clinically relevant therapeutic benefit in comparison to vehicle treatment. There is also compelling evidence and a high degree of certainty of the cost-effectiveness of Ikervis compared with artificial tears at the lowest cost-effectivenss threshold, of £20,000 per QALY gained.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

The brand name is Ikervis, approved name is ciclosporin. Ikervis belongs to the family of medicines called immunosuppressants.

1.2 What is the principal mechanism of action of the technology?

Ikervis® is a sterile, positively charged, oil-in water, unpreserved ophthalmic emulsion that contains ciclosporin (CsA) Ph Eur., a well-established immunomodulating substance, at a concentration of 1 mg/ml. The topical delivery of Ikervis is optimisetimd by excipients such as cetalkonium chloride (CKC), that act as a cationic agent.

In summary, CsA has an anti-inflammatory effect on the cornea and the lacrimal (tear) gland (23) 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) (1, 10, 11). It also increases tear secretion from the lacrimal gland by releasing neurotransmitters from sensory nerve endings, which interact with the parasympathetic nerves (28). The use of an ocular emulsion reduces the systemic toxicity of CsA and increases its

concentrations in the conjunctiva and cornea when compared to systemic administration.

More specifically, CsA inhibits the production and/or release of pro-inflammatory cytokines, and up-regulates the release of anti-inflammatory cytokines. All available evidence suggests that it acts specifically and reversibly on lymphocytes, does not depress hematopoiesis and has no effect on the function of phagocytic cells. (23)

Following ocular administration, CsA enters corneal and conjunctival infiltrated T-cells and through its binding to cyclophilin A, it inactivates the phosphatase calcineurin. CsA-induced inactivation of calcineurin inhibits the dephosphorylation of the transcription factor NF-AT and prevents its translocation into the nucleus, thus blocking the expression of anti-inflammatory cytokines such as IL-2 and the subsequent activation of the T-cell (28).

The emulsion comprises oil droplets stabilised by surfactants and dispersed in a continuous aqueous phase. A cationic surfactant is used to provide a positive charge to the oily droplets and to stabilise the emulsion system by achieving an electrostatic repulsion between the oil droplets. The emulsion formulation is specifically designed to prolong the residence time of each eye drop on the epithelial layer of the eye: the positively charged oil droplets adhere to the negatively charged surface moieties by electrostatic attraction (25). The cationic charge [brought by cetalkonium chloride (CKC)], is known to play an important role both in the emulsion stability and biological performances of the product (ocular absorption of CsA), and importantly, without acting as a preservative agent.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

A European Marketing Authorization Application for Ikervis was filed with the European Medicines Agency for the treatment of severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes, on 6th December 2013. Expected approval is the middle of April 2015.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

In the rapporteur and co-rapporteur day 150 joint response assessment report from the EMEA (CHMP list of questions), a major clinical objection was the lack of efficacy with regard to the primary endpoints in both Phase III studies (the SANSIKA and SICCANOVE trials) as there was no significant difference with Ikervis relative to vehicle (the comparator), in spite of improvement in secondary endpoints (signs of DED) and post-hoc analyses. In addition, the clinical significance of demonstrated efficacy in effects on clinical signs (Corneal Fluorescein Staining and HLA-DR [used to analyse expression of any marker by conjunctival epithelial cells, or identification of inflammatory and goblet cells]) was raised as a secondary issue.

The rapporteur and co-rapporteur comment that the failure to demonstrate efficacy with the primary endpoints may have been due to the heterogeneity and complexity of DED, and the well documented poor correlation between signs and symptoms. It could also be due to the change in the Ikervis formulation; as compared to the formulation used in SICCANOVE, the formulation used in SANSIKA contained CKC as an excipient, and no longer benzalkonium chloride (BAK).

Currently, there are no special conditions attached to the marketing authorisation for Ikervis.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The anticipated indication for Ikervis in the UK is the treatment of severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The post-SANSIKA study is a multicentre open label interventional prospective 24-month study (10 study visits), which includes patients that participated in the SANSIKA study (NVG10E117). This study should help understanding of the long-term effect of Ikervis since its main objective is to assess the sustainability of the effect following Ikervis discontinuation once the patient is markedly improved with respect to baseline in the main study, i.e. at least 2 grades on the modified Oxford scale, from CFS ≥ 4 to CFS ≤ 2. It is also expected to provide long-term safety data.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of availability in the UK is July/August 2015.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes, Temporary Authorization for Use (ATU) was achieved in France in October 2013 (First patient in: January 2014).

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yes, a submission to the Scottish Medicines Consortium is planned for the first quarter of 2015.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A2 Unit costs of technology being appraised

Pharmaceutical formulation	Active ingredient: ciclosporin Ph. Eur. (CsA) (0.1% w/w/) Excipient: Cetalkonium chloride (CKC)
Acquisition cost (excluding VAT)	£72
Method of administration	Topical (eye drop)
Doses	One drop of 1 mg/ml
Dosing frequency	Once daily at bedtime
Average length of a course of treatment	Historically, the average duration of treatment for DED ranges from 20 weeks (in Italy) to 52 weeks (Germany and Spain) (22). We do not anticipate that this would be substantially different for Ikervis.
Average cost of a course of treatment	The average cost of a course of treatment is unknown. In the economic modelling we have assumed that patients who have not responded by month 6 discontinue treatment.
Anticipated average interval between courses of treatments	The post SANSIKA trial has been designed to monitor the long-term efficacy and relapse rates in patients who have previously received Ikervis. This data is preliminary, but shows that the rate of recurrence of severe keratitis two years after cessation of the SANSIKA study is: • 28.8% (13/45) of patients treated 12M in SANSIKA with IKERVIS • 42.1% (8/19) of patients treated 6M in SANSIKA with IKERVIS 25% of the population has a time to relapse (back to CFS grade 4) at : • 336 days or less in patients treated 12M in SANSIKA with IKERVIS. • 175 days or less in patients treated 6M in SANSIKA with IKERVIS In the model we have assumed only one course of treatment.
Anticipated number of repeat courses of treatments	See above
Dose adjustments	None

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A. Ikervis is pharmaceutical technology.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

In accordance with the proposed indication, appropriate patient selection for Ikervis should be guided by treatment failure with adequate use of tear substitutes and DED severity. As patients who may be eligible for Ikervis are already in the treatment pathway, the determination of DED severity with additional tests or investigations after failure with adequate use of tear substitutes is likely to be performed with or without Ikervis as an additional treatment option. The frequency of self-administration of Ikervis which is topical by eye drop, is likely to be lower compared with that of standard eye drops, and administration of Ikervis by a healthcare professional is not required.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Because of the negligible rate of systemic absorption and the reversible action with CsA, with topical CsA there is no requirement for monitoring patients over and above usual clinical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Artificial tear eye drops may be administered at the same time as Ikervis. Concomitant use of unpreserved artificial tear eye drops was permitted in the confirmatory Phase III clinical trial SANSIKA supporting the approval of Ikervis, at the request of the patient. In contrast, concomitant medicinal products with possible influence on the tear film, tear secretion or ocular surface was prohibited.

However, considering all available data in the SANSIKA trial, there was a progressive decrease in the use of artificial eye drops over time in both treatment groups.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Ikervis will be used for dry eye disease (DED) (keratoconjunctivitis sicca), a multifactorial, chronic and progressive ophthalmic disease causing inflammation and damage to the ocular surface with increased osmolarity of the tear film(1, 2). 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.(29) DED is usually chronic, and no specific cure exists. Symptoms of DED include discomfort, visual morbidity or disturbance and tear film instability with potential damage to the ocular surface.(1, 3)

The symptoms of DED usually correlate poorly with the objective clinical findings such as corneal erosion, punctate keratopathy, epithelial defects, corneal ulceration (sterile or infected), corneal neovascularisation, corneal scarring, or even corneal perforation (4-7).

Complications associated with DED include conjunctivitis, corneal ulceration, and corneal infection (8). DED may also compromise results of corneal, cataract or refractive surgery (9).

Dysfunction of the ocular surface and the tear-secreting Meibomian gland, that usually maintain the tear supply and clear used tears, result in an unstable and poorly maintained tear film causing ocular signs and symptoms described above.(30) Subsequent dysregulation of native immune mechanisms leads to a cycle of continued inflammation, accompanied by changes in immune responses which characterize the chronicity of the condition as such, chronic inflammation is proposed as the core mechanism in the development and intensification of DED, (2, 31, 32).

Dysfunction may develop due to ageing, a decrease in supportive factors (such as hormones), systemic inflammatory diseases (such as rheumatoid arthritis or Sjögren syndrome) or ocular inflammatory disorders and local immune/autoimmune mechanisms (ocular surface antigens, autoantibodies, TH1/TH17 cells), ocular surface diseases (such as viral keratitis) or surgeries that disrupt the trigeminal afferent sensory nerves (e.g. LASIK), or medication (e.g. antihistamines, anticholinergics or antidepressants) that disrupt the efferent cholinergic nerves responsible for stimulating tear secretion.

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) (5, 10, 11). 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 (12). Treatment may also avoid the negative impact on functional visual acuity, resulting in impaired vision, ocular fatigue, inability to read or drive (13, 14).

DED severity is commonly assessed using subjective questionnaires, in conjunction with objective invasive and noninvasive assessments. The choice of assessment varies between jurisdictions and physicians.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The treatment of severe keratitis in adult patients with DED that does not improve despite treatment with tear substitutes is the only indication for this technology.

The overall prevalence of DED in the literature (all severities) varies widely, between 0.1%-27% in the USA, Australia, and Europe (33-35) depending on

the elicitation methods and diagnostic criteria used. To date, only one study has been carried out in the UK, estimating the prevalence of DED (all severities) to be 13.2% in clinically diagnosed patients (35). However, considering DED with severe keratitis, the literature is poor, Schaumberg (36, 37) reported a prevalence of severe DED in women (3.4%) and men (2.2%) in the US (a country-wide survey), while van Landingham (38) reported 3.1% among elderly residents (65-84 years) in the US. There were no estimates for the incidence and prevalence of severe keratitis in these populations.

Due to the paucity of formal prevalence and incidence estimates for patients with DED and severe keratitis, data reported by Schaumberg (2003), Schaumberg (2009) and Clegg (2006) were used to generate estimates of the incidence and prevalence of dry eye in England and Wales for the purposes of the submission (Schaumberg 2003; Clegg 2006; Schaumberg, 2003). There are no reports of the prevalence of severe DED in England, Wales, or in the UK in general.

In the absence of direct reports it has been estimated that 2.28% of the population experience DED of which 6% is severe. Based on a current adult population (18-90 yrs) in England and Wales of approximately 45 million patients (39) then this would approximate to an eligible population of ~61,000 patients, for more detail see section 8.1.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

There is no evidence that DED impacts life expectancy, therefore the average life expectancy of adults in England and Wales should be assumed. Based on data sourced from the ONS, the average life expectancy of men is 78.9 years, and women 82.7 years.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The NHS published a Clinical Knowledge Summary for Dry Eye Syndrome in 2008 which includes recommendations for the treatment of DED by severity subgroups (National Health Service 2008).

The advice provided for healthcare professionals who encounter patients with mild to moderate DED includes information on the use of tear-replacement therapy (artificial tears) and ointments where advice on environmental and lifestyle issues alone is insufficient (National Health Service 2008).

For people with severe DED, preservative-free artificial tears are described as being suitable, while an ocular lubricant ointment should be used at night (National Health Service 2008). Eye ointments containing paraffin may be uncomfortable and blur vision, so they should only be used at night and never with contact lenses. For people with visible strands of mucus, acetylcysteine drops (an artificial tears with mucolytic and lubricant properties, suitable for the relief of dry eye syndromes associated with deficient tear secretion, impaired or abnormal mucus production; marketed only in the UK) should be considered (National Health Service 2008).

Further to this, it is stated that “referral for treatment with active medication or surgery is seldom required”.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

In the UK, patients seeking medical advice for symptoms of DED are asked to visit their GP for examination (National Health Service 2012).(8) If symptoms are mild or moderate, or persist with treatment, or are severe, the GP will then refer cases to an optometrist or an ophthalmologist for diagnosis (NHS Prescribing Guidelines for Dry Eye 2013; Clinical Expert Interview with Professors Lightman and Figueiredo, 2014; National Health Service 2014). GPs would continue the management of the patient based on clinical notes

and recommendations from the ophthalmologist (Clinical Expert Interview with Professors Lightman and Figueiredo, 2014).

Optometrists diagnose and manage many patients with mild to moderate dry eye disease (Clinical Expert Interview with Professor Lightman, 2014). These practitioners do not require a referral and are not required to share information with the GP (Clinical Expert Interview with Professor Lightman, 2014). Optometrists also refer moderate to severe cases to ophthalmologists, via the GP (Clinical Expert Interview with Professor Figueiredo, 2014).

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).

Therefore, as Ikervis provides an additional option to other active treatments and surgery without the need for incremental specialist or technologically advanced monitoring or care, its availability will not alter the clinical pathway of care.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

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 (8). Many contain demulcents, which are polymers added to the formulation to enhance lubrication. These provide only short-term relief at best, and require frequent dosing throughout the day. Some brands (hypromellose) require administration in 30-minute intervals initially until symptoms improve. Other artificial tear products containing carbomers or polyvinyl alcohol require less frequent application but may be less well tolerated. Sodium chloride is short acting and suitable as 'comfort drops' or for use with contact lenses. In addition, the preservative in many artificial tear products often causes eye irritation due to an ingredient called benzalkonium chloride (BAK) and its epithelial toxic effects. BAK is frequently used preservative in topical ophthalmic preparations and topical lubricants. Its toxicity is related to the amount of tear secretion, the severity of the ocular

surface disease, and its concentration and frequency of use (International Dry Eye Workshop 2007). The NHS Prescribing Guidelines For Dry Eye Syndrome (2013) clearly state the need for a preservative-free formulation for patients with severe dry eye with ocular surface disease and impairment of lacrimal gland secretion, "…the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants. The ocular surface inflammation associated with dry eye is exacerbated by preserved lubricants …".

Patients with mild to moderate symptoms may also be treated symptomatically with lubricants for long periods of time. As lubricants are classified as 'health products', proof of their efficacy is not required by Health Authorities (15). Many are available over-the-counter.

The secretory oral drug pilocarpine has been shown to be effective in patients with DED due to Sjögren syndrome only (40).

Other therapeutic strategies, such as ocular inserts, occlusion of the lacrimal puncta, or anti-inflammatory treatment are available (NHS choices 2014). 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 (Sahin 2008; Ozcan 2007; Doan 2007) (11, 19). Intraocular pressure (IOP), which is increased in glaucoma, may develop in patients administered steroids (Razeghinejad 2012). More than 5% of patients respond to chronic topical steroid use with a severe increase in IOP, which requires medical or surgical intervention (Razeghinejad 2012). In addition, all patients taking topical corticosteroids in the long-term require regular monitoring of IOP and cataract formation (American Academy of Ophthalmology 2013). In spite of their known side effects, especially with long-term use, and lack of authorization for DED, topical corticosteroids are used frequently.

Clinical guidelines recommend using CsA as early as possible to avoid keratitis and its vicious circle (1) and for moderate DED only (American

Academy of Ophthalmology 2013). Use of CsA in ophthalmic preparations has been documented since 1985 and its safety profile appears acceptable. Based on the mechanism of action of CsA, it is likely that patients suffering from DED might receive benefit from CsA. 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. However, it is available in some EU Member States for compassionate use, such as in France on a named patient basis since 2006 to treat patients with DED of an immunological aetiology. Restasis is also used across Europe well beyond its FDA-approved indication as highlighted by a recent observational study. A recent qualitative observational study (41) has indicated that the use of hospital pharmacy compounded CsA formulation is widespread in clinical practice in Europe. It was observed that Restasis is used in more than 13 of the EU Member States and is even reimbursed by some social security systems.

Patients with more severe DED that can cause major ocular complications, such as infections or ulcers with irreversible loss of visual acuity, represent a group of patients with a worse prognosis (7) who are in need of more effective treatments (42). These patients with severe DED are trapped in a vicious cycle of inflammation and ocular surface injury.

2.7 Please identify the main comparator(s) and justify their selection.

In the absence of an approved and valid active comparator, the Ikervis excipient (vehicle) was used as a comparator in the clinical trial programme, as recommended by the European Medicines Agency (EMA). In the opinion of the EMA, there was no requirement to compare Ikervis with a standard treatment since no such treatment exists. Restasis, which is not registered in Europe and does not target severe keratitis, cannot be considered an

appropriate comparator for severe keratitis in DED. Artificial tears, which do not have any active properties and are usually the background treatment and bring temporary relief only, or corticosteroids, which are well known for their local side effects (cataract, glaucoma) when used chronically, were all discussed with the EMA, and subsequently ruled out. This approach was endorsed by the French Agency for the Safety of Health Products and the CHMP in scientific advices (June 2010 and December 2010 respectively).

In addition, comparison of Ikervis to its vehicle was deemed necessary since eye drop vehicles are known to have some beneficial effect on their own.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The safety profile for Ikervis in patients with severe DED is characterised by local ocular adverse reactions at instillation site (≤1/10, in accordance with the EMA classification) and common adverse reactions (≤1/100 to <1/10) including eye disorders only (meibomianitis, erythema of eyelid, lacrimation increased, ocular hyperaemia, vision blurred, eyelid oedema, conjunctival hyperaemia, eye irritation, eye pain). Non-severe adverse reactions in SANSIKA were managed by either temporary or permanent cessation of treatment and severe adverse reactions by permanent cessation of treatment. No further treatment was utilised in the management of adverse reactions.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As Ikervis is administered topically and in the patient's place of choice, there are no anticipated resource use implications for the NHS, other than the cost of Ikervis itself, due to location of care, staff usage, administration costs, monitoring and tests.

2.10 Does the technology require additional infrastructure to be put in place?

Additional infrastructure in the health service will not be required with the introduction of Ikervis.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

  Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

The Company is not aware of any negative issues relating to equality in NICE guidance resulting from this appraisal. As Ikervis will be available as a controlled formulation and therefore at the same quality throughout the UK, DED patients with severe keratitis will have equal access to a standard product.

3.1.2 How has the analysis addressed these issues?

N/A

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

Ikervis is innovative in its potential to make a significant and substantial impact on health-related benefits for DED patients with severe keratitis and therefore a poor prognosis with no available authorised active treatments with demonstrated efficacy and safety. The results of the Phase III programme demonstrate that compared to vehicle, once daily Ikervis provides a clear and sustained significant improvement of corneal staining, a significant reduction in ocular surface inflammation and a significant improvement in tear osmolarity. Ikervis also has a beneficial effect on symptoms. These eye-health benefits of Ikervis are important to clinicians who are interested in maintaining the integrity of the ocular surface knowing that in patients with DED, increased ocular surface disease usually correlates with reduced corneal sensation, and severe keratitis can lead to major ocular complications, such as infections, ulcers or corneal perforation with irreversible loss of visual acuity (7, 42). Severe keratitisis the main concern for ophthalmologists since it can lead to corneal ulceration and impaired vision. Therefore, treating severe keratitis and maintaining and protecting the integrity of the ocular surface is an important clinical challenge and deserves to be duly taken into consideration.

Ikervis can be considered a ‘step-change’ based on its profile as an authorised treatment with a fixed formulation manufactured to the highest quality in a controlled setting, in combination with the availability of evidence of efficacy and safety supporting its use. It is also innovative in comparison with artificial tears alone. Specifically, the active ingredient in Ikervis, CsA, provides immunosuppressive and anti-inflammatory effects for a disease that is considered to have an inflammatory component. However, while it is recognised that CsA is available in pharmacy-compounded preparations with varying and uncontrolled formulations of CsA (0.05 to 2.0%) with oil and

varied quality control standards, it is also without evidence of efficacy and safety from well-designed clinical trials. In contrast, Ikervis offers a fixed and therefore controlled formulation that ensued based on evidence from a Phase II programme. The ocular bioavailability of CsA with Ikervis is also higher than with other CsA formulations. Ikervis is also characterised by its clinical efficacy and safety profile in sufficient depth and breadth to determine that it is suitable and tolerable for treating severe keratitis in DED and to provide ample prescribing information for physicians, considering their patients' complex health histories, medical conditions, and their variety of concomitant medications.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The incremental health-related benefits of Ikervis, relative to vehicle, are driven by objective outcomes associated with eye health including corneal staining, ocular surface inflammation and tear osmolarity. However, as discussed previously, symptoms correlate poorly with objective clinical findings (4-7) and are unlikely to be captured fully in the QALY calculation Equally the long term implications of a reduction in ocular surface inflammation and other objective improvements are unlikely to be captured in the QALY calculation, which currently assumes a conservative long term benefit for responders to both Ikervis and artificial tears.

In addition, the benefit of related to once daily dosing of one drop compared to, for example, a drop every half hour required with some artificial tear products, is also unlikely to be included in the QALY calculation.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

The judgements made in 4.1.1 and 4.1.2 above ensue from the Phase III programme, specifically, the SANSIKA and SICCANOVE trials.

The results of the SANSIKA are as follows:

- A significant improvement of corneal staining over time as shown with the secondary endpoint related to Corneal Fluorescein Staining, with a significant effect at Month 6 (p= 0.037), and as early as Month 3 (p=0.024).

- Both Ikervis and the vehicle were efficacious on symptom improvement.

- The reduction in ocular surface inflammation was significantly better with Ikervis compared to vehicle at Month 6 (p= 0.021) and as early as Month 1 (p= 0.019).

- A significant improvement in tear osmolarity was seen at Month 6 in favour of Ikervis (p= 0.048). Tear osmolarity was assessed as an exploratory variable in a post hoc analysis using osmolarity values above 308 mOsms/L.

The SANSIKA study confirmed the results of the SICCANOVE study:

- There were no between groups differences in symptoms of discomfort and visual disturbance; there was a similar marked improvement with both Ikervis and vehicle

- Ikervis resulted in a statistically significantly greater reduction in damage to the ocular surface compared with vehicle (p=0.009)

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
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.	The decision problem reflects the approved indication for Ikervis. Patients with severe keratitis are a recognised subgroup of severe DED patients.
Intervention	Ciclosporin (CsA)	Ciclosporin (CsA)	N/A
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)	The decision problem addressed in the submission does not vary substantially from the scope. However, in the absence of an approved and valid active comparator, the Ikervis excipient (vehicle) was used as a comparator in the clinical trials, as recommended by the European Medicines Agency (EMA). In the opinion of the EMA, there is no standard or authorized active treatment for severe DED or severe keratitis.Artificial tears do not have any active properties and are usually the

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			background treatment, or corticosteroids, which are well known for their local side effects (cataract, glaucoma) when used chronically, were all discussed and ruled out. This approach was endorsed by the French Agency for the Safety of Health Products and the CHMP in scientific advices (June 2010 and December 2010 respectively). In addition, comparison of Ikervis to its vehicle was deemed necessary since eye drop vehicles are known to have some beneficial effect on their own.
Outcomes	• eye pain and discomfort • symptoms of dry eye disease (including photosensitivity, ability to open eyes, visual acuity and ability to concentrate) • adverse effects of treatment • health-related quality of life.	• Corneal staining (CFS) using modified Oxford scale • Oxford Surface Disease Index (OSDI) • CFS-OSDI responder (a patient satisfying the following conditions simultaneously: change from baseline in CFS ≤-2 and in OSDI ≤-30%) • ocular discomfort (using a visual analogue scale (VAS)) • inflammation (HLA-DR)	Regulatory guidance recommended studying both signs and symptoms of the disease. Objective outcomes such as inflammation, ocular surface disease, corneal staining and tear osmolarity were also evaluated in the Phase III programme to determine the impact of Ikervis on eye health to provide additional clinically relevant information. For example, severe inflammation is the main concern for ophthalmologists since it can lead to corneal ulceration and impaired vision. Therefore,

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
		• tear film osmolarity • Tear film break up time • Symptoms: burning, stinging, foreign body sensation, itching, eye dryness, pain, blurred vision or sticky feeling, photophobia (each assessed by a VAS) • adverse effects of treatment • health-related quality of life	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.
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 the 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.	N/A
Subgroups to be considered	If the evidence allows, a subgroup analysis of people with Sjogren syndrome should be considered.	A subgroup analysis of patients with Sjogren syndrome has been presented in the clinical efficacy section.	In SANSIKA, approximately one third of the population had Sjögren's syndrome, including 58 patients in the Ikervis arm and 34 in the vehicle arm.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	Guidance will only be issued in accordance with the marketing authorisation.		It was not considered feasible to conduct a cost-effectiveness analysis on this small subset of patients.
Special considerations, including issues related to equity or equality			

Section B– Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same	5.12

	weight regardless of the other characteristics of the individuals receiving the health benefit	
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

To identify full publications, searches were conducted on the 21st July 2014 in MEDLINE®, MEDLINE® In-process, Embase (all OVID SP) and CENTRAL. In addition, a search of PubMed was conducted to identify E-publications ahead-of-print. Search strategies combined indexed and free text terms for dry eye disease and the treatments outlined in the decision problem. Designated filters to identify randomised controlled trials were used in MEDLINE® and Embase.

To identify unpublished literature three conference proceedings were searched: the Association for Research in Vision and Ophthalmology annual meeting (2014), the European Society of Ophthalmology annual meeting (2013) and the World Ophthalmology Congress annual meeting (2014). Phase 2 and 3 Clinical study reports for Ikervis® were provided by Santen.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1 Eligibility criteria used in search strategy

Inclusion Criteria	
Patients	• Adult patients (≥18 yr) with severe keratitis with dry eye disease (DED) which has not improved despite treatment with tear substitutes
Intervention	• Ciclosporin-A (NOVA22007; Ikervis®)
Comparators	• Ciclosporin-A (CsA) • Punctual plugs • Permanent punctual occlusion • Autologous serum • Artificial tears • Cholinergic agonists • Acetylcysteine drops • Topical Corticosteroids
Outcomes	Efficacy outcomes • Corneal fluorescein staining (CFS) score assessed with the Oxford(43)/modified Oxford scale(44)[1], 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

[1] The Oxford Scale was first proposed by AJ Bron in 1997 (The Doyne Lecture: Reflections on the tears. *Eye* (1997) 11:583-602). The Modified Oxford Scale was updated by SANTEN after request from CHMP/SAWP in 2006.

	• Investigator global evaluation of efficacy Safety outcomes • Aadverse 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)
Other	• No restrictions on language or publication date were applied • Studies must have had a treatment or observation duration of at least 1 week • There must been at least 20 patients included in the study analysis • Studies including only newly diagnosed DED patients were excluded

During full publication review discrepancies in the reporting of patient severity were noted. To ensure consistency across the studies, we used the DEWS 2007 dry eye severity grading scheme to identify studies recruiting severe DED patients (grade 3 or 4). A number of studies pre-dated the publication of DEWS 2007 or used alternative diagnostic measures; in these cases two of the three the following criteria had to be fulfilled for inclusion in the review:

- a Schirmer test score (with or without anaesthesia) ≤5 mm/ 5min (DEWS grade 3 or 4)
- a TBUT test score ≤5 seconds (DEWS grade 3 or 4).
- an OSDI of ≥ 23 (0 -100 scale) (SANSIKA inclusion criteria)

If disease severity was unclear the study was excluded.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the

statement should equal the total number of studies listed in section 6.2.4.

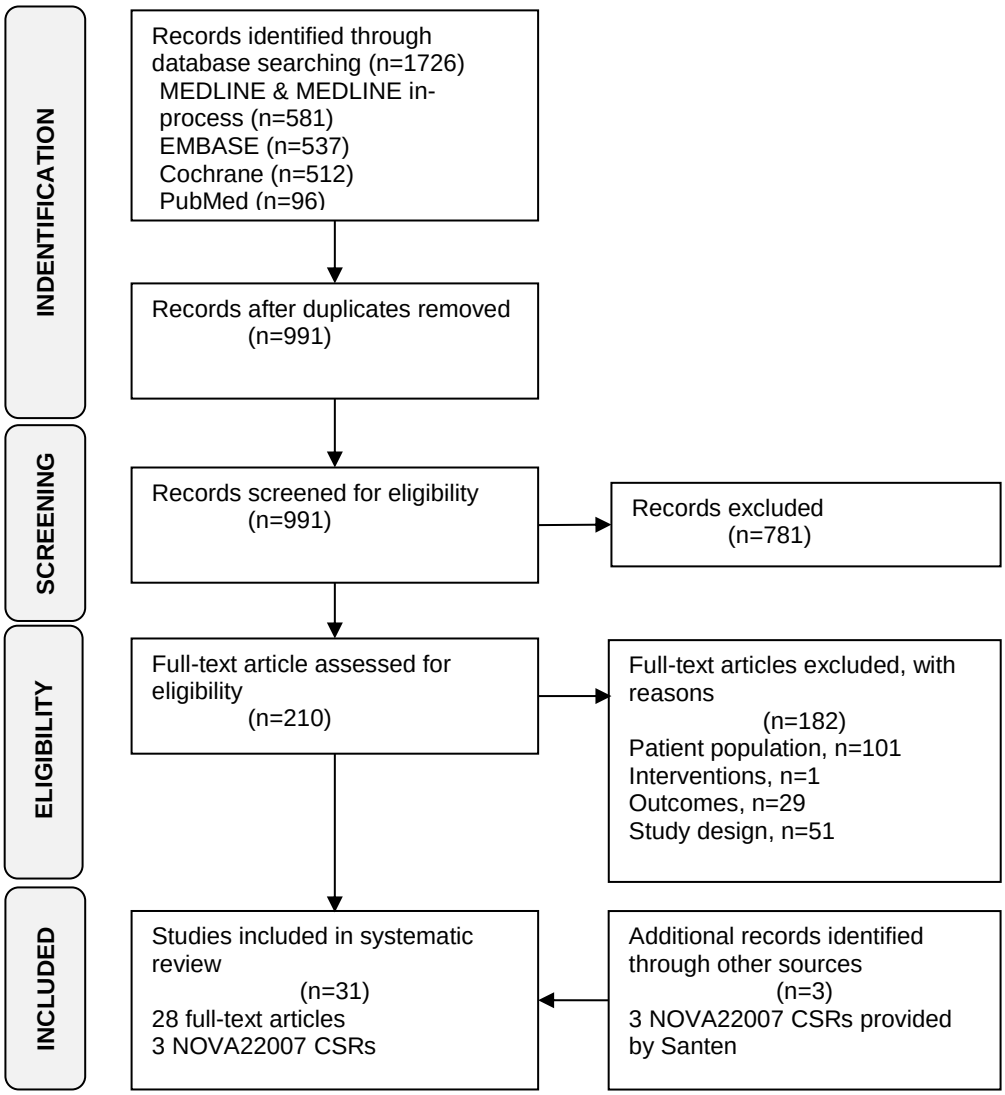


Figure B1: PRISMA Diagram for Systematic Review

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Not applicable.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list

must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

As stated in paragraph 6.2.1, disease severity was inconsistently reported in the identified trials. We specified three criteria that studies had to meet for inclusion in the review. Where study inclusion criteria did not specify at least two of these criteria, baseline values were used to assess the severity of DED patients. Twenty-five included studies stated at least two of the criteria in their study inclusion criteria or reported mean baseline values demonstrating that patients fulfilled at least two of these criteria.

There were three studies which did not sufficiently use the criteria but were included because of other measures used to classify study patients as having severe DED: Jackson (2011) only reported TBUT, but was included because study inclusion criteria (TBUT ≤3 seconds) and baseline values were indicative of very severe patients. Sall (2000) and Grene (1992) only reported Schirmer test values (≤ 5 mm/min), however these studies were included because their inclusion criteria specified patients with high CFS scores. Grene (1992) also states that “56 patients with severe keratoconjunctivitis sicca were enrolled”.

A list of relevant RCTs is provided below

Table B2 List of relevant RCTs

Trial ID	Interventions/Comparators										Primary Study ref
	Anti-inflammatory				Artificial Tears		Punctual Plugs	Vehicle	Autologous Serum	Other	
Amparo 2013	Anakinra 2.5%	Anakinra 5%	-	-	-	-	-	1% carboxymethyl cellulose	-	-	(45)
Burgess 2008	-	-	-	-	-	-	Punctal plugs (silicone) Punctal plugs (SmartPlugs)	-	-	-	(46)
Celebi 2014	-	-	-	-	Carboxymethylcellulose Sodium 0.5% (Refresh)	-			20% AS	-	(47)
Cho 2013	-	-	-	-	-	-	-	-	• 100% AS • 50% AS + saline • 50% AS + 0.3% sodium hyaluronate • 50% AS + 0.5% ceftazidime	-	(48)

Trial ID	Interventions/Comparators										Primary Study ref
	Anti-inflammatory				Artificial Tears		Punctual Plugs	Vehicle	Autologous Serum	Other	
Grene 1992	-	-	-	-	Carboxymethylcellulose (CMC) 1%	Hydroxypropylmethylcellulose (HMC)	-	-	-	-	(49)
Jackson 2011	Medical food supplement (Tears Again HYDRATE) + CsA (Restasis®)	-	-	-	Medical food supplement (Tears Again HYDRATE)		-	-	-	-	(50)
Jee 2014	-	-	-	-	Preservative-free 0.1% sodium hyaluronate, 0.1% fluorometholone and 0.05% CsA (Restasis®)	Preserved 0.1% sodium hyaluronate, 0.1% fluorometholone and 0.05% CsA (Restasis®)	-	-	-		(51)
Kim 2009	CsA 0.05% (Restasis®) + AT	-	-	-	0.5% carboxymethylcellulose sodium (Refresh Plus)		-	-	-	Retinyl palmitate 0.05%, polysorbate 80 1% + AT	(52)
Kinoshita 2012	-	-	-	-	-	-	-	-	-	• Placebo • Rebamipide 1% • Rebamipide 2%	(53)
Kinoshita 2013	-	-	-	-	Sodium hyaluronate 0.1%		-	-	-	Rebamipide 2%	(54)
Kojima	-	-	-	-	preservative-free		-		AS	-	(55)

Trial ID	Interventions/Comparators										Primary Study ref
	Anti-inflammatory				Artificial Tears		Punctual Plugs	Vehicle	Autologous Serum	Other	
2005											
Lee 2014	-	-	-	-	0.1% hyaluronic acid		-	-	-	Thermal massager	(56)
Liu 2012	Pranoprofen 0.1% + sodium hyaluronate 0.1%	-	-	-	Sodium hyaluronate 0.1%		-	-	-	-	(57)
Matsumoto 2012	-	-	-	-	-	-	-	-	-	• Placebo • Diquafosol 1% • Diquafosol 3%	(58)
Matsuo 2002	-	-	-	-	Saline (Trehalose 100 mM control)	Saline (Trehalose 200 mM control)	-	-	-	• Trehalose 100 mM • Trehalose 100 mM	(59)
Matsuo 2004	-	-	-	-	-	-	-	-	-	• Hyaluronan-containing eye drops > trehalose 100 mM • Trehalose 100 mM > hyaluronan-containing eye drops • Hydroxyethylcellulose-containing	(60)

Trial ID	Interventions/Comparators										Primary Study ref
	Anti-inflammatory				Artificial Tears		Punctual Plugs	Vehicle	Autologous Serum	Other	
										eye drops > trehalose 100 mM • Trehalose 100 mM > hydroxyethylcellulose-containing eye drops	
Ono 2004	-	-	-	-	-	-	-	-	-	• Placebo • Cevimeline 20 mg • Cevimeline 30 mg	(61)
ORA 2009	CsA (NOVA22007) 0.05%	CsA (NOVA22007) 0.1%	-	-	-	-	-	ophthalmic cationic emulsion	-	-	(62)
Papa 2001	-	-	-	-	AT (Hypotonic)	AT (Isotonic)	-	-	-	-	(63)
Qin 2013	-	-	-	-	-	-	-	-	-	• Partial SMG transplantation • Total SMG transplantation	(64)
Qiu 2013	-	-	-	-	carbomer gel and bFGF		Smart PLUG500 thermosensitive punctal			-	(65)

Trial ID	Interventions/Comparators										Primary Study ref
	Anti-inflammatory				Artificial Tears		Punctual Plugs	Vehicle	Autologous Serum	Other	
							plugs				
Rabensteiner 2013	-	-	-	-	-	-	Punctal plugs (collared silicone) Punctal plugs (SmartPlugs)			-	(66)
Sall 2000	CsA 0.05% (Restasis®)	CsA 0.1% (Restasis®)	-	-	-	-	-	Vehicle		-	(67)
SANSIKA 2013	CsA (NOVA22007) 1mg/mL	-	-	-	-	-	-	ophthalmic cationic emulsion		-	(68)
SICCANOVE 2013	CsA (NOVA22007) 0.1%	-	-	-	-	-	-	ophthalmic cationic emulsion		-	(69)
Song 2011	-	-	-	-	Sodium hyaluronate eye drops		-	-	-	Fuming tablet + sodium hyaluronate eye drops	(70)
Stevenson	CsA	CsA	CsA	CsA	-	-	-	Vehicle		-	(71)

Trial ID	Interventions/Comparators										Primary Study ref
	Anti-inflammatory				Artificial Tears		Punctual Plugs	Vehicle	Autologous Serum	Other	
2000	0.05% (Restasis ®)	0.1% (Restasis ®)	0.2% (Restasis ®)	0.4% (Restasis ®)							
Takamura 2012	-	-	-	-	Sodium hyaluronate 0.1%		-	-	-	Diquafosol 3%	(72)
Tian 2014	-	-	-	-	Sodium hyaluronate 3 g/L	Sodium hyaluronate 1 g/L + recombinant human EGF eye drops	-	-	-	-	(73)
Wan 2013	-	-	-	-	Dextran and hypromellose eye drops		-	-	-	Qiming granules + dextran and hypromellose eye drops	(74)
Watson 2010	-	-	-	-	-	-	-	-	-	• Placebo • Therapeutic Ocular Surface Medium	(75)

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Three trials were identified including NOVA22007 as an intervention: the phase 2 ORA trial and two phase 3 trials, SICANNOVE and SANSIKA. In each trial NOVA22007 was compared to vehicle. SANSIKA recruited severe keratitis and severe DED patients defined as a CFS score of 4 on the modified Oxford Scale, a Schirmer score (without anaesthesia) ≥2 mm and <10 mm and an OSDI score of ≥ 23. SICCANOVE recruited moderate-to-severe DED patients defined as a CFS score of 2 to 4 (modified Oxford Scale), a Schirmer score (without anaesthesia) ≥2 mm and <10 mm and TBUT score of ≤8 s. Patients recruited into the ORA study had a more mild DED that those recruited into the two phase 3 trials (CFS ≥2, Schirmer ≥1 mm and ≤10 mm).

In reference to the decision problem, the SANSIKA trial most closely represents the population of interest.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

A great deal of heterogeneity was observed in how severity has been defined and the types of comparator treatments received in the published literature. The NOVA22007 trials all compared NOVA22007 to vehicle; other trials identified in the systematic review also included comparisons to vehicle, however these were not considered homogenous to the vehicle used in the NOVA22007 trials. The patient population recruited into the SANSIKA trial appeared to be the only trial which clearly defined patients with severe keratitis and severe DED. No other trials identified in the systematic review appeared to clearly include patients with the same level of disease severity.

To address the decision problem it was believed that the most appropriate trial available was the SANSIKA trial of NOVA22007 versus vehicle in patients with severe keratitis and severe DED. Evidence from SANSIKA was supplemented with evidence from the SICCANOVE trial of NOVA22007 versus vehicle in patients with moderate-to-severe DED. No other trials identified by the systematic review were considered (a copy of the full systematic review has not been included in the appendices but is available on request).

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Not applicable.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The

following tables provide a suggested format for when there is more than one RCT.

Background and objectives

NOVA22007 1mg/ml is a new eye drop emulsion to treat adult patients with severe dry eye disease (DED) also known as keratoconjunctivitis sicca. The current tradename is IKERVIS® and previous tradename of is Cyclokat®. Ciclosporin A (also known as CsA) is a lipophilic cyclic polypeptide that has been used for several decades as a systemic immunosuppressant and has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor (TCGF). It is also known to up-regulate the release of anti-inflammatory cytokines. As it is well recognized that inflammation has a prominent role in the development and amplification of the signs and symptoms of DED, Ciclosporin may offer a more long-term solution than many of the currently available DED treatments, including artificial lubricants. Furthermore, hospital pharmacy compounded ophthalmic CsA is already widely used in clinical practice across Europe.

Mild-moderate DED patients can usually be treated symptomatically with tear substitutes for long periods of time, although few successful treatments exist for those with moderate-severe DED. With a lack of appropriate and valid active comparator, studies involving NOVA22007 have been designed to assess whether NOVA22007 on top of tear substitutes is superior to its vehicle in the treatment of DED adult patients with severe keratitis that does not improve despite treatment with tear substitutes.

The clinical development program for NOVA22007 was designed primarily to compare the efficacy, safety and tolerability of NOVA22007 with its vehicle, identified as a negative control. The initial Phase IIa study compared three doses of NOVA22007 (0.025%; 0.05% and 0.1%), with safety and tolerability as the primary objective. The secondary objective was to examine the pharmacodynamic, dose effect relationship of NOVA22007. The Phase IIB ORA study was designed to provide information for the dose to be used in further studies; NOVA22007 0.05% and 1% were compared to the vehicle and both objective and subjective parameters were assessed using a Controlled

Adverse Environment (CAE), a technologically advanced clinical model that provides a standardized approach to studying investigational treatments of dry eye. These studies are not discussed further.

The Phase III SICCANOVE study was designed to assess the efficacy of NOVA22007 on signs and symptoms used as co-primary endpoints after 6-month treatment. The trial population included a broader demographic spread in terms of disease severity than that of the proposed label claim. SICCANOVE had two primary objectives – a superiority comparison against vehicle at 6 months as measured by the change from baseline in CFS score (using the modified Oxford scale) and a superiority comparison at the same time-point against vehicle as measured by change in global score of ocular discomfort unrelated to study medication.

Clinical data generated in the first 3 studies were used to design the additional Phase III study, the SANSIKA study. This primary objective (Part 1) of this study was to compare the efficacy of NOVA22007to its vehicle on a background of tear substitutes over 6 months it also assessed the long-term safety of NOVA22007 over a 12 month period (Part 2). The main study (Part 1) was designed to encompass clinically relevant aspects of DED and its current guideline-recommended treatment. This included the enrolment of a well-defined patient population with severe keratitis reflecting that of clinical practice and the use of sponsor-provided artificial tears. By including a further 24 week open-label extension study following the SANSIKA study (Part 2), the long-term efficacy of NOVA22007 over 12 months could be assessed.

The safety profile for repeated dosing of NOVA22007 was also an objective for the study programme. In particular, the potential systemic risks of ciclosporin were assessed, along with other effects, with the aim to create a full safety profile to judge the balance of risk and benefit.

Key features of the SICCANOVE and SANSIKA studies are summarised in Table B3.

Table B3 Comparative summary of methodology of the RCTs

Trial no. (acronym)	Phase III SICCANOVE (NVG06C103)	Phase III SANSIKA (NVG10E117)
Location	France, Germany, Italy, Czech Republic, Spain, UK	France, Germany, Italy, Czech Republic, Spain, UK, Belgium, Sweden, Austria
Design	A phase III, multicentre, randomized, controlled, double-masked trial of NOVA22007 (ciclosporin 0.1%) ophthalmic cationic emulsion versus vehicle in patients with moderate to severe dry eye syndrome.	A multicenter, randomized, double-masked, 2 parallel arm, vehicle-controlled, 6-month phase iii trial with a 6 month open label treatment safety follow-up period to evaluate the efficacy and safety of IKERVIS® (Cyclokat®) 1 mg/ml (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe dry eye disease.
Duration of study	6 months	6 months
Method of randomisation	Central randomisation (1:1) stratified by presence/absence of Sjogren's syndrome	Computerized randomization scheme stratified by center
Method of blinding (care provider, patient and outcome assessor)	Double-masked	Double-masked
Intervention(s) (n =) and comparator(s) (n =)	Intervention(n=1): NOVA22007 0.1% Comparator (n=1): Vehicle (NOVA22007 minus active pharmacologic agent)	Intervention(n=1): NOVA22007 0.1% Comparator (n=1): Vehicle (NOVA22007 minus active pharmacologic agent)
Primary outcomes (including scoring methods and timings of assessments)	CFS (Modified Oxford Scale), ocular discomfort score. Measured at week 0 (baseline), week 4, week 12 and week 24.	CFS (Modified Oxford Scale) and OSDI score combined into one single score (see section 06.3.5). Measured at week 0 (baseline), week 4, week 12 and week 24.
Secondary outcomes (including scoring methods and timings of assessments)	FCS, LGCS, Schirmer-I, ocular discomfort VAS, TBUT, OSDI questionnaire, Global efficacy, artificial tear usage.	CFS, OSDI score, ocular discomfort VAS, Schirmer-I, use of artificial tears, investigator global evaluation of efficacy, LGCS, TBUT, HRQoL (NEI-VFQ-25 and EQ-5D), HLA-DR expression, tear film osmolarity, Aes.
Duration of follow-up	n/a	A 6 month extension to the study was used to assess the long term safety of treatment with Ikervis

Methods

SICCANOVE: A phase III, multicentre, randomized, controlled, double-masked trial of NOVA22007 (ciclosporin 0.1%) ophthalmic cationic emulsion versus vehicle in patients with moderate to severe DED.

SANSIKA: A multicenter, randomized, double-masked, 2 parallel arm, vehicle-controlled, 6-month phase III trial with a 6 month open label treatment safety

follow-up period to evaluate the efficacy and safety of NOVA22007 1 mg/ml (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe DED.

Design

The Phase III SICCANOVE study and the Phase III confirmatory SANSIKA study included patients with moderate to severe DED or severe DED respectively.

Study enrolment started for SICCANOVE in September 2007 and was completed in September 2009, during which time 492 patients were randomised to treatment. For SANSIKA, study enrolment was started in July 2012 and was completed in February 2013, during which time 246 patients were randomised to treatment.

Assessment of efficacy was made only with the “worst eligible eye” defined as:

- For SICCANOVE: it was the eye with the highest modified Oxford score for corneal staining at baseline; in case both eyes had the same degree of corneal staining, the right eye was considered.
- For SANSIKA: it was the eye with the highest lissamine green staining score at baseline. If both eyes had the same lissamine green staining score at baseline, the eye with the worse Schirmer test score at baseline was to be used. If both eyes had the same Schirmer test score at baseline than the right eye was to be used.

Discontinuation of study treatment or withdrawal from the study occurred upon voluntary discontinuation; missed visits; lack of efficacy of the study drug according to the investigator; ocular intolerance or AEs necessitating discontinuation from the study; lost to follow up; other investigator or sponsor decision. Discontinued patients were not replaced. Patients discontinued for AE(s) were followed-up until the event resolved or was considered medically

stable by the Investigator. If a patient discontinued at a scheduled visit or an unscheduled visit, all the tests of the Final Visit were to be performed.

Method of randomisation

SICCANOVE: Patients were randomly assigned to one of the two treatment groups using a 1:1 randomisation scheme provided by the Interactive Voice Response System (IVRS). Randomization was centralised and was stratified by the presence/absence of Sjögren's syndrome.

SANSIKA: Patients were randomised using a computerised randomisation scheme (2:1) using blocks of 6 treatments and centralised using an Interactive Voice Response System (IVRS). Randomisation was stratified by centre.

Masking

Patients were masked as to treatments. Masking was achieved by providing the study medication (test medication and vehicle) in identical masked treatment units and by identifying each study medication by a treatment number. For SICCANOVE and the first six months of the SANSIKA study (Part 1), the study medication was double-masked, with the Investigator, sight personnel, sponsor representatives and any personnel involved in monitoring, data management or any other aspects of the study being masked to the study treatment. In the second 6 months of the SANSIKA study (Part 2), the study treatment was open label. Although the study treatment with NOVA22007 was unmasked in the final 6 months of the study, the Investigators, staff, and patients had to remain masked to the prior randomised treatment assignments until all patients had completed the 12 month study. The Investigator was entitled to break the masking codes if a SAE occurred and masking information would influence the patient's management. Breaking of the mask automatically disqualified the patient from further study participation.

Intervention and placebo

In the SICCANOVE and SANSIKA studies, patients were randomised to one of two treatment groups; NOVA22007 0.1% or placebo (NOVA22007 vehicle).

After the 6-month study period in the SANSIKA study, patients were all assigned to the NOVA22007 0.1% treatment group for a further 6-month safety follow-up period.

Patients were prescribed one drop once daily at bedtime of their assigned treatment (dose determined in IIa studies) to be self-administered. The instillation was conducted at the site on the days of study visits. The 0.1% eye drop formulation given once daily was chosen for further assessment in Phase III studies as this dose represented the appropriate balance between efficacy and safety concerns, including potential systemic ciclosporin effects. NOVA22007 and vehicle were packaged in polyethylene single-dose containers that were protected by an aluminium pouch package. If necessary, in order to control symptoms of DED, patients could use unpreserved artificial tears as needed, but not within 30 minutes before or after use of the investigated product, or not within 2 hours before a scheduled visit. Unpreserved artificial tears were provided by the Sponsor.

If a patient missed a scheduled dose, they were to continue to take their next dose as normal and were not to take 2 doses at the same time. Patient compliance was assessed by the number of used and unused containers of study medication in relationship to the duration of the follow-up interval.

Follow up

For both SICCANOVE and SANSIKA, patients were assessed for eligibility during a screening visit 7-14 days before baseline and study visits took place at baseline (month 0), month 1 and month 3. An additional study visit took place at month 6 for patients. For Part 2 of the SANSIKA study, study visits took place at month 9 and month 12.

Assessments and examinations carried out at study visits are reported in detail in Section 6.3.5.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the

eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

For both SICCANOVE and SANSIKA, patients with DED with different levels of disease severity were enrolled. The proposed target population for NOVA22007 is patients with severe keratitis or corneal lesions that do not improve despite adequate treatment with lachrymal substitutes.

In the SICCANOVE study, the exclusion/inclusion criteria were broadly comparable to the ones used in SANSIKA. The study population only differs from the proposed label in terms of disease severity since this study included a broader patient population. To be included into the study patients had to have a moderate to severe DED ≥2 on the modified Oxford scale with moderate to severe symptoms rated ≥2 on a 4-point semi-quantitative scale. The OSDI was used as a secondary variable to measure symptoms. In this study, patients were allowed to use standardised lachrymal substitutes provided by the company, at a capped dose of 6 drops per day.

The population included in SANSIKA reflects the proposed target patient population. Patients included in SANSIKA had a severe and well-defined DED, with corneal staining graded 4 on the modified Oxford scale, a Schirmer test scored between 2 and less than 10 mm/5 minutes and a symptom score ≥ 23 on the OSDI. In these patients, DED had lasted for more than 9 years on average, and lachrymal substitutes had been taken for quite a long time without providing a substantial improvement since most of them (90%) had a specific treatment (e.g., lachrymal substitutes) prior to study randomisation. In this study, patients were allowed to use standardised lachrymal substitutes provided by the company, when needed.

Table B4 Eligibility criteria in the RCTs

Trial no.	Phase III SICCANOVE (NVG06C103)	Phase III SANSIKA (NVG10E117)
Inclusion criteria	1. Male or female patients, aged ≥18 years. 2. At the baseline, moderate to severe dry eye condition persisting despite conventional management (which may have included artificial tear drops, gels or ointments and punctual occlusion), and defined as the following: • At least one moderate to severe symptom of dry eye with a score ≥2 (severity graded on a 4-point scale) i.e., burning/stinging, foreign body sensation, itching, eye dryness, pain, blurred vision or sticky feeling and photophobia, AND • Tear break-up time (BUT) ≤8 seconds AND • Corneal fluorescein staining ≥2 and ≤4 (modified Oxford scale, scale 0-5), AND • Schirmer tear test without anaesthesia of ≥2 mm/5 min and <10 mm/5 min, AND • Lissamine green staining >4 (Van Bijsterveld scale, scale 0-9). The same eye (eligible eye) was to fulfil all the above criteria. 3. Patient provided written informed consent. 4. Patient was willing and able to undergo and return for scheduled study-related examinations	1. Male or female aged 18 years and over. 2. Persistent severe DED at the Screening and Baseline Visits defined as the following: • CFS score of 4 on the modified Oxford scale, AND • Schirmer test without anesthesia scored ≥2 mm/5 min and <10 mm/5 min, AND • OSDI score ≥23. 3. Provision of written informed consent, prior to any study-specific procedures. 4. The same eye (eligible eye) had to fulfill all applicable above criteria.
Exclusion criteria	1. Best corrected distance visual acuity (BCDVA) score> + 0.7 LogMar in the eligible eye. 2. Dry eye resulting from the destruction of conjunctival goblet cells or scarring.	*Ocular Conditions/Diseases* 1. CFS grade 5 or below 4 on the modified Oxford scale. 2. DED resulting from the destruction of

Trial no.	Phase III SICCANOVE (NVG06C103)	Phase III SANSIKA (NVG10E117)
	3. Abnormal lid anatomy or blinking function. 4. Abnormalities of the nasolacrimal drainage system. 5. Presence or history of any systemic or ocular disorder or condition, including ocular surgery, trauma or disease that could possibly interfere with the interpretation of study results. 6. Any relevant ocular anomaly interfering with the ocular surface, including post radiation keratitis, Stevens-Johnson syndrome, corneal ulcer history or concomitant corneal ulcer of infectious origin, etc. 7. Any ocular surgery or laser (including palpebral, refractive and cataract surgery/laser) within 6 months before study entry in the eligible eye and within 3 months prior to study entry in the non-eligible eye. 8. History of ocular trauma, infection (viral, bacterial, fungal), or ocular inflammation (Tyndall ≠ 0), not associated with KCS within the 3 months before the Screening visit. 9. Patients with severe blepharitis not related to dry eye or Sjögren syndrome, acute lesions of rosacea and/or progressive pterygium. 10. Any other ocular diseases requiring topical ocular treatment during the study period. 11. Presence or history of ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye. 12. Active or history of ocular herpes. 13. History of malignancy in the last 5 years (with the exception of basal cell carcinoma and cervix carcinoma). 14. Systemic disease not stabilized within 1 month before the Screening Visit (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease) or judged by the Investigator to be incompatible with the study (e.g. current systemic infections) or	conjunctival goblet cells or scarring. 3. Any relevant ocular anomaly other than DED interfering with the ocular surface including trauma, post radiation keratitis, Stevens-Johnson syndrome, corneal ulcer history, etc. 4. Abnormal lid anatomy, abnormalities of the nasolachrymal drainage system or blinking function in either eye. 5. Anticipated use of temporary punctal plugs during the study. Patients with punctal plugs placed prior to Screening were eligible for enrolment; however, punctual plugs must have remained in place during the study. 6. Active herpes keratitis or history of ocular herpes. 7. History of ocular trauma or ocular infection (viral, bacterial, fungal, protozoal) within 90 days before the Screening Visit. 8. History of non-infectious ocular inflammation not associated with dry eye (e.g. uveitis, scleritis, peripheral ulcerative keratitis). 9. Any ocular diseases other than DED requiring topical ocular treatment during the course of the study. Patients taking benzalkonium chloride (BAK)-free IOP lowering medications were eligible for study enrolment. 10. Severe blepharitis and/or Meibomian gland disease (MGD). Patients enrolled with mild to moderate blepharitis and/or MGD had to be treated as appropriate during the study. 11. Active rosacea and/or progressive pterygium. 12. History of ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye. 13. Use of contact lenses during the study. 14. Any prior refractive surgery (i.e., laser in situ keratomileusis [LASIK], laser epithelial keratomileusis [LASEK], photorefractive keratectomy [PRK], etc.). These procedures were not allowed during the course of the study. 15. Ocular laser/surgery other than

Trial no.	Phase III SICCANOVE (NVG06C103)	Phase III SANSIKA (NVG10E117)
	condition incompatible with the frequent assessments needed by the study. 15. Known hypersensitivity to one of the components of the study or procedural medications (fluorescein, lissamine green, oxybuprocaine, etc). 16. Presence or history of severe systemic allergy. 17. Any change, within 1 month prior to study entry, of systemic medication that could affect a dry eye condition (e.g., oestrogen-progesterone or other oestrogen derivatives (only for post-menopausal women), antihistamines, tricyclic antidepressants, anxiolytics, antimuscarinics, beta-blocking agents, phenothiazines, omega-3, systemic corticosteroids, etc. These treatments were allowed during the study provided they remained stable throughout the course of the study 18. Use of systemic or topical CsA (i.e., Restasis®), tacrolimus or sirolimus, within 6 months prior to study entry. 19. Use of topical corticosteroids or prostaglandins within 1 month before study entry. 20. Any change, within 1 month prior to study entry, of systemic pilocarpine, isotretinoine or tetracycline, as well as the use of topical pilocarpine or isotretinoine within 1 month before study entry. The systemic treatments (pilocarpine, isotretinoine or tetracycline) were allowed during the study provided they remained stable throughout the course of the study. 21. Use of topical anti-histaminics, dual agents, beta-blocking agents or antibiotics within 2 weeks before study entry. 22. Any change in systemic immunosuppressant drugs within 1 month before study entry. 23. Any concomitant topical ocular treatment other than the study medications and concomitant tear substitute provided. 24. Contact lens wearing during the	refractive surgery (including palpebral and cataract surgery) within 90 days before the study. Elective ocular laser/surgery was not allowed during the course of the study. 16. BCDVA score ≥+1.0 logarithm of the minimum angle of resolution (LogMAR) (≤35 early treatment diabetic retinopathy study □ETDRS□ letters, ≤20/200 Snellen or ≤0.1) in each eye. *Ocular Treatments* 17. Use of topical CsA (e.g. Restasis®), tacrolimus or sirolimus within 90 days before the Screening Visit. These treatments were also prohibited during the course of the study. 18. Use of topical corticosteroids, antibiotics, pilocarpine, antihistamines, or BAKpreserved IOP lowering medications within 30 days before the Screening Visit. These treatments were also prohibited during the course of the study. 19. Use of any artificial tears other than those provided by the study Sponsor during the course of the study. *Systemic Conditions/Diseases or Treatments* 20. Any change within 30 days before the Screening Visit or anticipated change during the course of the study in the dose of systemic medications that could affect a dry eye condition (e.g., estrogen-progesterone or other estrogen derivatives [only for post-menopausal women], pilocarpine, isotretinoine, tetracycline, antihistamines, tricyclic antidepressants, anxiolytics, antimuscarinics, beta-blocking agents, phenothiazines, omega-3, systemic corticosteroids, etc.). These treatments were allowed during the study provided they remained stable throughout the course of the study. 21. Disease not stabilized within 30 days before the Screening Visit (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections) or judged by the Investigator to be incompatible with the study. 22. Presence or history of severe systemic allergy. 23. Any change in systemic

Trial no.	Phase III SICCANOVE (NVG06C103)	Phase III SANSIKA (NVG10E117)
	study. 25. Anticipated use of temporary punctum plugs during the study. Prior punctal plugs were allowed provided they were inserted at least 1 month before study entry and they remained in situ during the study. 26. Any planned refractive surgery (laser in situ keratomileusis [LASIK], laser epithelial keratomileusis [LASEK], photorefractive keratectomy [PRK], etc) during the course of the study. 27. Pregnancy or lactation at study entry. 28. Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as implants, injectables or oral contraceptives together with condoms, some intra-uterine devices, sexual abstinence or vasectomised partner) throughout the conduct of the study up to 2 weeks after study end. The post-menopausal women (2 years without menstruation) do not need to use any method of birth control. 29. Presence or history of drug addiction or alcohol abuse. 30. Patient who had participated in a clinical trial with a new active substance during the past month before study entry. 31. Participation in another clinical study at the same time as the present study.	immunosuppressant drugs within 30 days before the Screening Visit or anticipated change during the course of the study. 24. Known hypersensitivity to 1 of the components of the study or procedural medications (e.g., fluorescein, lissamine green, etc.). 25. History of malignancy in the last 5 years. 26. Pregnancy or lactation at the Baseline Visit. 27. Women of childbearing potential not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomized partner) throughout the conduct of the study treatment periods and up to 2 weeks after the study end. Post-menopausal women (two years without menstruation) did not need to use any method of birth control. *Compliance/Administrative* 28. History of drug addiction or alcohol abuse. 29. Presence or history of any systemic or ocular disorder, condition, or disease that could possibly have interfered with the conduct of the required study procedures or the interpretation of study results. 30. Participation in a clinical trial with an investigational substance within the past 30 days. 31. Participation in another clinical study at the same time as the present study.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

SANSIKA study**-** The SANSIKA study population represents the target DED population well with respect to demographic characteristics. In SANSIKA Part 1 (see Table B5), patients were predominantly female (91.2%), a gender

distribution typical for DED. The study population involved patients from 8 different countries in Europe, with a mean age of 61.3 years. One third of the patients reported Sjögren's syndrome.

CFS score at Baseline was 4.00 in all patients, in accordance with the inclusion criteria of the study protocol. Mean OSDI score at baseline was similar in both treatment groups; 61.4 with NOVA22007 and 58.8 with vehicle. Mean global VAS assessment score at Baseline was similar in both treatment groups; (55.6mm vs. 54.5mm). Mean Schirmer test score at Screening was similar in both treatment groups; 3.7mm/5 min vs. 3.9mm/5 min.

With respect to demographic and baseline characteristics, the treatment groups were generally well balanced. The similarities between treatment groups validate and reflect the process of randomisation, thus minimising bias and ensuring independence of observations.

In SANSIKA Part 2 (open label follow up), demographic and baseline characteristics of patients were similar to those included in Part 1 (see Table B5). Mean age at the Month 6 Visit was similar in patients assigned to NOVA22007 (60.8 years) and with vehicle (62.1 years). Most patients were females in both treatment groups (80.5% vs. 92.4%). The proportion of patients who had Sjögren's syndrome was similar in patients assigned to NOVA22007 (39.1%) and to vehicle (40.5%).

SICCANOVE study- In SICCANOVE (see Table B5), and overall similar to SANSIKA, there were more females (84.5%) than males (15.5%) in the study. Most of the patients were Caucasian (98.8%). In addition, the NOVA22007 group included 3/241 Black patients (1.2%); whilst the Vehicle group included 2/248 Black patients (0.8%) and 1/248 Asian patient (0.4%) Overall one third had a Sjögren's syndrome with the distribution similar between treatment groups, as it was a stratification factor. The mean age was 58.2 years (range 20 to 90 years) for the 2 treatment groups (means of 57.6 years vs. 58.8 years).

Mean CFS scores were comparable at Baseline in both treatment groups (2.83 vs. 2.80), as were mean ocular discomfort scores as measured using

the VAS, at Baseline in both treatment groups (47.12 vs. 43.84). Mean OSDI scores at baseline were also comparable (41.96 vs. 44.41).

Overall, there were no major differences in demographic and main comorbidity data between treatment groups, and the full and per-protocol analysis sets showed a similar profile to the safety analysis set. The number of elderly patients and women is considered adequate for assessment of efficacy.

Table B5 Characteristics of participants in RCTs SICCANOVE and SANSIKA across randomised groups

	Phase III SICCANOVE (NVG06C103) N=489		Phase III SANSIKA (NVG10E117) Part 1 (N=245)		Phase III SANSIKA (NVG10E117) Part 2 (N=207)	
Trial no. (acronym) Baseline characteristic	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%**	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%)**	**Vehicle/ Ciclosporin (NOVA22007) 0.1%**	**Ciclosporin (NOVA22007) 0.1%/ Ciclosporin (NOVA22007) 0.1%**
	n=248	**n=241**	**n=91**	**n=154**	**n=79**	**n=128**
Age						
Mean (SD)	58.8 (12.7)	57.6 (12.9)	62.1 (11.8)	60.8 (13.5)	62.1 (12.19)	60.8 (13.94)
Median	60	57.0	63.5	61.7	63.5	61.74
(Min, Max)	(21,87)	(20, 90)	(33, 87)	(23, 88)	(33,86)	(23,88)
Gender (n, %)						
Male	40 (16.1)	36 (14.9)	8 (8.8)	28 (18.2)	6 (7.6)	25 (19.5)
Female	449 (83.9)	205 (85.1)	83 (91.2)	126 (81.8)	73 (92.4)	103 (80.5)

	Phase III SICCANOVE (NVG06C103) N=489		Phase III SANSIKA (NVG10E117)		Phase III SANSIKA (NVG10E117)	
			Part 1 (N=245)		Part 2 (N=207)	
Trial no. (acronym) **Baseline characteristic**	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%**	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%)**	**Vehicle/ Ciclosporin (NOVA22007) 0.1%**	**Ciclosporin (NOVA22007) 0.1%/ Ciclosporin (NOVA22007) 0.1%**
Race (n, %) Caucasian Black Asian Other	 245 (98.8) 2 (0.8) 1 (0.4) -	 238 (98.8) 3 (1.2) - -	Not collected	Not collected	Not collected	Not collected
Sjögren syndrome (n, %) Yes No	 88 (33.5) 160 (64.5)	 89 (36.9) 152 (63.1)	 34 (37.4) 57 (62.6)	 58 (37.7) 96 (62.3)	 32 (40.5) 47 (59.5)	 50 (39.1) 78 (60.9)
Time since DED diagnosis (years) Mean (SD) Median (Min, Max)	 8.0 (8.4)	 7.2 (6.8) 5.1 (0.1, 38.3)	 9.7 (6.7)	 8.8 (7.1)	Not collected	Not collected

	Phase III SICCANOVE (NVG06C103) N=489		Phase III SANSIKA (NVG10E117) Part 1 (N=245)		Phase III SANSIKA (NVG10E117) Part 2 (N=207)	
Trial no. (acronym) Baseline characteristic	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%**	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%)**	**Vehicle/ Ciclosporin (NOVA22007) 0.1%**	**Ciclosporin (NOVA22007) 0.1%/ Ciclosporin (NOVA22007) 0.1%**
	5.2 (0, 64.1)		8.7(0.2, 30.7)	6.2 (0.2, 31.5)		
Corneal staining Mean (SD) Median (Min, Max)	 2.80 (0.72) 3.00 (2, 5)	 2.83 (0.71) 3.00 (2, 4)	*Inclusion criteria for this study of FCS score=4.0* 4.0 (0.0) 4.0 (4,4)	*Inclusion criteria for this study of FCS score=4.0* 4.0 (0.0) 4.0 (4,4)	Not collected	Not collected
Schirmer-I test Mean (SD) Median (Min, Max)	 4.58 (2.42) 4.00 (1, 10)	 4.64 (2.88) 4.00 (0,25)	 3.92 (2.17) 3.00 (2,9)	 3.69 (2.02) 3.00 (2,9)	Not collected	Not collected
TBUT score					Not collected	Not collected

	Phase III SICCANOVE (NVG06C103) N=489		Phase III SANSIKA (NVG10E117)		Phase III SANSIKA (NVG10E117)	
			Part 1 (N=245)		Part 2 (N=207)	
Trial no. (acronym) **Baseline characteristic**	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%**	**Vehicle**	**Ciclosporin (NOVA22007) 0.1%)**	**Vehicle/ Ciclosporin (NOVA22007) 0.1%**	**Ciclosporin (NOVA22007) 0.1%/ Ciclosporin (NOVA22007) 0.1%**
Mean (SD) Median (Min, Max)	3.90 (1.71) 3.50 (1,9)	3.80 (1.64) 3.67 (0,9)	3.51 (1.72) 3.00 (0.0, 8.5)	3.29 (1.56) 3.00 (1.0,7.3)		
OSDI score Mean (SD) Median (Min, Max)	41.96 (21.84) 39.58 (0,100)	44.41 (21.94) 45.23 (0,100)	58.77 (18.36) 58.33 (25.0,100.0)	61.44 (19.41) 62.50 (25.0,100.0)	Not collected	Not collected
VAS score Mean (SD) Median (Min, Max)	43.84 (19.98) 43.88 (0,92.1)	47.12 (19.20) 46.19 (0,95.4)	54.49 (18.45) 52.50 (16.9,92.5)	55.55 (20.61) 55.13 (5.0,98.0)	Not collected	Not collected

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B6 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Secondary outcome(s) and measures
Phase III SICCANOVE (NVG06C103)	• Co-primary, at Month 6: Change in CFS (modified Oxford Scale) • Co-primary, at Month 6: Change in Global Score of ocular discomfort from baseline (VAS)	• Change in CFS (modified Oxford scale) at Month 1&3 • Change in Lissamine green staining (Van Bijsterveld scale) at Month 1, 3&6 • Change in Schirmer's tear test at Month 3&6 • Change in each symptom of ocular discomfort unrelated to study medication (VAS scale) at Month 6 • % of responders based on improvement in ocular symptoms (VAS) at Month 6 • Change in TBUT at Month 1, 3 & 6 • Change in OSDI at Month 1, 3& 6 • % of complete responders [a] at Month 6 • Global evaluation of efficacy by the Investigator at Month 1, 3 & 6 • Average number of times per day of AT used the week preceding the visits at Month 1, 3 & 6 • Number of days where AT were not used the week preceding the visits at Month 1, 3 & 6 • Impression cytology at baseline and at Month 6 (subset of 70 patients in selected study centres)
Phase III SANSIKA (NVG10E117)	Composite responder at Month 6: CFS-OSDI (signs & symptoms) Response defined as an improvement of ≥2 points in CFS AND an improvement by ≥30% in OSDI	*At Month 6*: • CFS improvement of ≥2 points (Oxford modified scale) • OSDI response: improvement of ≥ 30% • Improvement of ≥30% global ocular discomfort (VAS) • CFS improvement ≥2 points and global ocular discomfort improvement (VAS) ≥30% *At Months 1&3:* CFS-OSDI composite response *At Months 1, 3 and 6:* • Change in CFS • Change in OSDI • Change in global ocular discomfort (VAS) • Change in Lissamine Green total score (Van Bijsterveld scale)

Trial no. (acronym)	Primary outcome(s) and measures	Secondary outcome(s) and measures
		• Use of artificial tears. *At Month 6:* • Schirmer test • Investigator global evaluation of efficacy *Other secondary endpoints:* • TBUT at Month 6 • HLA-DR expression at Months 1&6 • Tear Film Osmolarity at Months 1&6 • QoL (NEI-VFQ and EQ-5D) at Month 6

[a] complete clearance of corneal fluorescein staining - AT: artificial tears - CAE: controlled adverse environment - CFS: corneal fluorescein staining - OSDI: Ocular Surface Disease Index - QoL: quality of life - OPI: Ocular protection index - TBUT: Tear break-up time - VAS: visual analogue scale Reliability/validity/current use in clinical practice

The efficacy endpoints for the trials were selected according to the expected effect of CsA in patients with DED. The scales and instruments, which were used either as primary or secondary endpoints, are detailed further below.

Primary endpoints

Corneal Fluorescein Staining (CFS)

Throughout the NOVA22007 clinical program, the primary pharmacodynamic measure of ciclosporin's effect was the Corneal Fluorescein Staining (CFS) measured in the SANSIKA study with the Modified Oxford grading scale. This scale was also used in the Phase III SICCANOVE study.

In general, punctate staining of the cornea is not normal and the presence of punctate staining with fluorescein suggests the loss of epithelial cell membrane or junctional integrity. The modified Oxford scale uses a 7-point ordinal scale (0, 0.5 and 1 to 5) consisting of a series of panels labelled A to E in order of increasing severity. A CFS graded 0 represents complete corneal clearing. In the SANSIKA study, only patients with a CFS graded 4 were to be included. The CFS was assessed at every study visits. A negative change from Baseline indicated an improvement.

Reliability/ validity/ current use in clinical practice- CFS measured using the modified Oxford scale is standard clinical practice for the diagnosis of DED (21).

Ocular discomfort

In the SANSIKA study, symptoms were assessed as part of the primary endpoint with a validated scale, the Ocular Surface Disease Index (OSDI). This scale was also used in SICCANOVE as a secondary variable to assess patient's symptoms. In the SICCANOVE study, symptoms unrelated to study medication instillation were assessed using a global score of ocular discomfort, which was the mean of eight individual symptoms (burning/stinging; itching; foreign body sensation; blurred vision; eye dryness; photophobia; pain and sticky feeling) assessed via VAS.

The OSDI is a 12-item self-administered PRO questionnaire to assess ocular surface symptoms. The OSDI has an overall score and 3 subscale scores: ocular symptoms (3 items), vision-related function (6 items), and environmental triggers (3 items). Each OSDI item is scored on a Likert-type scale ranging from 0 to 4 points, where 0 indicates none of the time and 4 all of the time. The OSDI overall and subscale scores range from 0 (normal ocular surface) to 100 (complete disability). The OSDI score was measured at every study visit. A negative change from baseline indicated an improvement in vision-related functioning.

The self-administered Visual Analog Scale (VAS) was used to assess global symptoms of ocular discomfort that was unrelated to instillation of the study medication. The global VAS assessment of ocular discomfort was the average of the main 8 symptoms: burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia, pain, and sticky feeling. The 8 symptoms were assessed in each eye and the data were used to calculate the global VAS assessment for both eyes. The global VAS assessment was expected to confirm the findings obtained with the OSDI questionnaire. VAS ranges from 0% to 100%, and was measured at every study visit from the

baseline Visit. A decrease in the global VAS assessment of ocular discomfort from baseline indicated improvement.

Reliability/ validity/ current use in clinical practice- The OSDI has been tested for reliability and validity, and can effectively discriminate between normal, mild to moderate, and severe dry eye disease as defined by both physician's assessment and a composite disease severity score (1) It is commonly used in DED patients and recommended by the regulatory authorities.

The CHMP advised in their 2006 final advice that the use of the VAS to assess global ocular discomfort was preferable to individualising the most bothersome symptom at each evaluation (Santen CHMP discussions, Data on file)

SANSIKA primary endpoint

In contrast to SICCANOVE where CFS and ocular discomfort were assessed separately, the primary efficacy variable for SANSIKA was the *CFS-OSDI response* at Month 6, which is a composite variable combining the CFS response and the OSDI response.

A CFS-OSDI responder was defined as a patient satisfying simultaneously the following conditions:

- Improvement of 2 points or more from Baseline in CFS in the analysis eye (i.e. change in CFS ≤-2), AND
- Improvement by 30% or more from Baseline in OSDI (i.e. % change ≤-30%).

Secondary endpoints

Use of concomitant artificial tears

The use of artificial tears (provided by the Sponsor) was monitored throughout the studies. After the Screening Visit, patients were allowed to instill one unpreserved artificial teardrop in each eye as often as needed to ameliorate their dry eye symptoms in the SANSIKA study, and up to six times a day in

the SICCANOVE. Patients were instructed not to use the unpreserved artificial tears: i) within 30 minutes before or after the use of the study medication, and ii) within 2 hours before the scheduled visit.

In the SICCANOVE study, patients were queried about their artificial tear usage at each visit. The compliance regarding the time interval between artificial tears instillation and study drug instillation was also queried. In the SANSIKA study, at every visit (except Screening), the used/unused bottles of the unpreserved artificial tears were collected. The number of artificial tears used per day in the analysis eye was estimated as: Weight of used artificial tears / [0.03 x 2 x (date of visit-date of previous visit)], in which the weight of used artificial tears was calculated as the difference in weight of unused and used artificial tear bottles during the period, and assuming that 1 g of artificial tears contains 33.3 drops.

Reliability/ validity/ current use in clinical practice- Artificial tears are the current gold standard clinical treatment for DED and can effectively relieve the symptoms of DED for a limited time. It is therefore reasonable to expect that study patients will use artificial tears to relieve DED symptoms experienced during the study period.

Investigator global evaluation of efficacy

At every study visit, the effect of the study medication on improvement of the patient’s DED was assessed by the Investigator at each centre, using a 4-point Likert scale (0 = Unsatisfactory; 1 = Not very satisfactory; 2 = Satisfactory; 3 = Very satisfactory).

Reliability/ validity/ current use in clinical practice- Investigator global evaluation is commonly used in clinical studies to provide a clinical view as to whether the treatment has been a success or a failure, according to a visual evaluation by the investigator.

Schirmer Test (without anesthesia) in both eyes

Schirmer Test was used in all studies to assess lacrimal secretion. Schirmer test was performed 15 minutes after CFS and/or lissamine green staining tests. Normal values are 9 to 18 mm of wetting. The test measures the volume of the tear lake and not the tear flow. A positive change from the baseline value (obtained at Screening) indicated improvement.

Reliability/ validity/ current use in clinical practice- Schirmer test has been commonly used to assess endpoint variables in ophthalmic clinical studies for several decades and moderate repeatability has been shown in DED.(76) The test is routinely used in clinical practice in the US and Germany and whilst still used in the UK it is not routine practice due to the time taken to perform the test. It should also be noted that whilst the Schirmer test is considered important, it does not correlate well with patient symptoms and as such has limited value despite having reasonable reproducibility.

Human Leukocyte Antigen-DR (HLA-DR) Expression on the Conjunctival Cell Surface by Impression Cytology

Impression Cytology is a non-invasive technique to remove ocular surface layers. Expression of the HLA-DR antigen on the surface of conjunctival epithelial cells is associated with dry eye syndrome. HLA-DR expressions on the conjunctival cell surface (quantified in Arbitrary Units of Fluorescence [AUF] and in percentages of HLA-DR+ conjunctival cells, presenting an expression of the inflammatory marker HLA-DR [HLA-DR+ cells]) were measured.

In SANSIKA, impression cytology was performed after instillation of one drop of oxybuprocaine 0.4% and at least 15 minutes after completion of CFS and/or lissamine green staining assessments. This was also tested in a subset of the population (n= 70) involved in SICCANOVE study (at Baseline and month 6).

Reliability/ validity/ current use in clinical practice- Impression cytology is commonly used in clinical studies and in lab-based environments. Although the technique is fairly straightforward, it is not practical in an active clinical

practice as it requires facilities to stain the specimens and a microscope to interpret and grade them.

Tear Break-Up Time (TBUT) in in Both Eyes

The TBUT test is used to assess tear film stability is the fluorescein BUT. In this method, a grid is projected onto the cornea and the amount of time to distortion of the image is measured.

In the NOVA22007 program, Tear Break-Up Time (TBUT) was performed after instillation of 5 µL of a 2% preservative-free sodium fluorescein solution into the inferior conjunctival sac of each eye. The TBUT was measured twice within the first minute after the instillation of the fluorescein, and a third time if the first 2 readings differed by more than 2 seconds. The average TBUT value was recorded (if longer than 10 seconds, 10 seconds was recorded). Values less than 5 seconds are indicative of significant DED. A positive change from baseline indicated improvement.

Reliability/ validity/ current use in clinical practice- TBUT is the most widely used method in clinical studies and in clinical practice to assess tear film stability and is generally recognised as reliable, especially when performed by an experienced practitioner (1).

Corneal and conjunctival Staining assessed using the Van Bijsterveld grading system (Lissamine Green Staining)

Lissamine green staining was performed after the assessment of the CFS with the slit lamp (16X magnification) in all three studies to assess the extent and severity of dryness of the cornea. The Van Bijsterveld grading system was used, which assesses three areas in each eye the nasal and temporal bulbar conjunctiva and the cornea. The intensity of lissamine green staining is graded on a scale from 0 to 3 for each area. The maximum value of staining for each eye is 9. Staining values of 3 or higher are considered abnormal. The lissamine green total score was defined as the sum of the scores for the temporal bulbar conjunctiva, the corneal area, and the nasal bulbar conjunctiva. A negative change from Baseline indicated an improvement.

Reliability/ validity/ current use in clinical practice- Diagnosis and assessment of DED using Lissamine Green Staining is commonly used in clinical practice and clinical studies, and is recognised as being reliable and accurate. (77)

Tear Film Osmolarity in Both Eyes

Tear film osmolarity, which assesses the composition and stability of the tear film structure, was an exploratory procedure in SANSIKA that was not performed on all patients. Hyperosmolarity of the tear film is recognized as an important pathogenetic factor in DED. In the SANSIKA study, tear film osmolarity was only assessed in centres that had access to the TearLaBOsmolarity System for the evaluation of patients with DED. A negative change from the Baseline Visit indicated an improvement.

Reliability/ validity/ current use in clinical practice- Hyperosmolarity testing has been hampered in the past by difficulties in tear collection and analytic procedures that required laboratory facilities. Difficulties are partly addressed with the TearlaBOsmolarity System which is a user-friendly instrument that only needs tiny volumes for analysis and determines hyperosmolarity semi-automatically. However, issues have been identified, such as technical problem with the Tearlab, reflex tearing, or the difficulty in establishing a dry eye diagnosis, which render the results difficult to interpret; therefore the measure is not routinely used in clinical practice.

Quality of Life Questionnaires

In the SANSIKA study, the following QoL questionnaires were completed:

- National Eye Institute Visual Function Questionnaire (NEI-VFQ-25);
- EuroQol 5D Questionnaire (EQ-5D).

The NEI-VFQ-25 is a questionnaire designed to measure vision-specific quality of life (QoL) of patients with visual impairments. The NEI-VFQ-25 consists of 25 items and takes about 10 minutes for the patient to complete. The 25 items are grouped into the following subscales: general vision (1 item), ocular pain (2 items), difficulty with near-vision activities (3 items), difficulty

with distant-vision activities (3 items), limitations in social functioning due to vision (2 items), mental health symptoms due to vision (4 items), role limitations due to vision (2 items), dependency on others due to vision (3 items), driving difficulties (2 items), limitations with color vision (1 item), limitations with peripheral vision (1 item), and 1 widely accepted general health item.

The self-administered format of NEI-VFQ-25 was used, unless local language translations were not available, in which case the NEI-VFQ-25 was administered by a health care professional. Each item was scored 0–100, with higher scores indicating better vision-targeted QoL. Each of the 12 scale score was calculated as the average of all items in the given scale. Missing items were not scored. A scale score could be generated if at least 1 item was answered. A NEI-VFQ-25 composite score was calculated as the average of the 11- vision-related scale scores (excluding general health). A positive change from baseline indicated an improvement.

The EQ-5D is a simple but effective standardized instrument designed for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care. There are 2 parts to this questionnaire: the health state classification consisting of 5 questions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression; generating a “summary index”) and the visual analogue scale thermometer (generating an EQ-5D VAS score, from 0: worst imaginable health state to 100: best imaginable health state). The self-administered format of EQ-5D was used, unless the patient was unable to complete the questionnaire, in which case the EQ-5D was administered by a health care professional and read out loud to the patient verbatim. A positive change from Baseline indicated an improvement.

Reliability/ validity/ current use in clinical practice- The NEI-VFQ-25 has been shown to be valid and reliable in DED (78) and is used in many trials and is well validated. The EQ-5D is widely used as a measure of QoL assessment in clinical studies and, whilst it is not as sensitive as ophthalmology-specific

measures, it has shown to be able to discriminate between DED severity groups.(79)

Treatment compliance

Treatment compliance was measured in the following ways during the two studies:

SICCANOVE Study- The patient (or legal representative(s)) was questioned regarding their compliance with the dose regimen of study medication (once daily in the evening in both eyes, at bedtime) at each study visit after Day 0. Overall compliance was defined as: *number of days with instillation / number of days in the study *100.* The Investigator recorded each return of unpreserved artificial tears, in order to verify the compliance of the patients

SANSIKA Study- Treatment compliance was assessed by the number of used and unused containers of study medication in relationship to the duration of the follow-up interval. The following formula was used for Part 1 and Part 2: *Compliance = (number of days with instillation1 / exposure)*100*. Compliance was calculated for each of the following periods:

- Part 1: Baseline to Month 1, Month 1 to Month 3, and Month 3 to Month 6;
- Part 2: Month 6 to Month 9 and Month 9 to Month 12.

Safety endpoints

Safety variables measured in both SANSIKA and SICCANOVE studies included adverse events (AEs) with separate analyses performed for ocular and systemic AEs. AEs were documented according to Event term, Severity, Expectedness and Relationship to study treatment. Data on Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), AEs of Special Interest (AESI) and Suspected Unexpected Serious Adverse Reaction (SUSAR) were also collected. Other safety variables included Best Corrected Distance Visual Acuity (BCDVA) to measure improvement or decline in vision, Intraocular Pressure (IOP), Blood Sampling for CsA Levels to assess

systemic absorption and Vital signs. External ocular examination and undilated biomicroscopy were performed at every visit to assess tolerability.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Analysis populations

In both NOVA22007 studies, the statistical analyses were performed based on the following patient populations:

- *Full Analysis Set (FAS)*: the FAS was introduced for the Phase III studies, as defined in ICH Topic E9 (CPMP/ICH/363/96) and included all randomized patients who received any amount of the study drug and for whom post-baseline data were available. The FAS is as complete as possible and as close as possible to the ITT 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.

- *Safety Analysis Set* (SAS) or Safety population: the SAS considered all randomized patients for whom there was any evidence they used study medication.

In both studies, the primary population for efficacy hypotheses was the FAS, where patients were analysed according to their randomised treatment group. Table B 7 and Table B 8 show the populations analysed in each study.

The majority of randomised patients (>95%) were valid for both the safety and efficacy analyses. The proportion of SANSIKA patients continuing treatment into the open-label phase was >80% and sufficient to assess long-term safety and the maintenance of efficacy observed in Part 1.

Table B 7 Populations analysed- SICCANOVE

	Number (%) Patients		
	NOVA22007	**Vehicle**	**Total**
Analysed by treatment as randomized			
Final Database[a]	245	250	495
Full Analysis Set (FAS)[b]	241 (98.0)	248 (99.2)	489 (98.8)
Number of patients excluded from the FAS (not treated/randomised in error)	4 (1.6)	2 (0.8)	6 (0.2)
Safety Analysis Set (SAF)[c]	242 (98.4)	250 (100.0)	492 (99.2)
Number of patients excluded from the SAF (not treated/LTFU)	4 (1.6)	0 (0.0)	4 (0.8)
Number of patients re-included in the SAF (not randomised but received treatment)	1 (0.4)	0 (0.0)	1 (0.2)

[a] Final database: all patients who signed the informed consent document, were randomized and retained in the data analysis.

[B]Full Analysis Set (FAS): all randomized patients who received any amount of the study drug.

[c] Safety Analysis Set (SAF): all randomized patients for whom there is any evidence they used study medication and for whom any follow-up data were available.

Table B 8 Populations analysed- SANSIKA Part 1 and Part 2

	Number (%) Patients		
	NOVA22007/ NOVA22007	**Vehicle/ NOVA22007**	**Total**
Part 1 (0-6 months)- Randomised, Double-Masked Treatment Period			
Analysed by treatment as randomized			
Final Database[a]	155 (100.0)	91 (100.0)	246 (100.0)
Full Analysis Set (FAS)[b]	154 (99.4)	91 (100.0)	245 (99.6)
Number of patients excluded from the FAS (not treated/no post-Baseline data)	1 (0.6)	0 (0.0)	1 (0.4)
Analysed by actual treatment received			
Final Database[a]	156 (100.0)	90 (100.0)	246 (100.0)
Safety Analysis Set (SAF)[c]	154 (98.7)	90 (100.0)	244 (99.2)
Number of patients excluded from the SAF (not treated/LTFU)	2 (1.3)	0 (0.0)	2 (0.8)
Part 2 (6-12 months)- Open Label Treatment Safety Follow-Up			
Analysed by actual treatment received during Part 1			
Final Database[a]	156 (100.0)	90 (100.0)	246 (100.0)
Full Analysis Set-OPEN (FAS-OPEN)[d]	128 (82.1)	79 (87.8)	207 (84.1)
Number of patients excluded from the FAS-OPEN (not treated)	1 (0.6)	0 (0.0)	1 (0.4)
Safety Analysis Set-OPEN (SAF-OPEN)[e]	128 (82.1)	79 (87.8)	207 (84.1)
Number of patients excluded from the SAF-OPEN (not treated)	1 (0.6)	0 (0.0)	1 (0.4)
Part 1 and Part 2 (0-12 months)- Entire Study			
Final Database	156 (100.0)	90 (100.0)	246 (100.0)
SAF patients who received NOVA220007 during Part 1[f]	154 (98.7)	N/A	N/A

[a] Final database: all patients who signed the informed consent document, were randomized and retained in the data analysis.

[B]Full Analysis Set (FAS): all randomized patients who received any amount of the study drug.

[c] Safety Analysis Set (SAF): all randomized patients for whom there is any evidence they used study medication and for whom any follow-up data were available.

[d] Full Analysis Set-OPEN (FAS-OPEN): all patients included in the FAS who were still treated at the Month 6 Visit and had available data for CFS and OSDI at Month 6.

[e] Safety Analysis Set-OPEN (SAF-OPEN): all randomized patients for whom there was any evidence they used study medication after Month 6 and for whom any follow-up data were available after the Month 6 Visit.

[f]The safety analyses from Month 0 to 12 were performed in the SAF patients who received NOVA22007 during Part 1.

Missing data

For the efficacy analysis in both studies, the Last Observation Carried Forward (LOCF) method was used to impute missing values. The imputation could have included baseline values. This method is likely to be conservative

in DED as the condition of the patients was expected to improve with both treatments considering the lubrication action of the Vehicle and patients in the experimental group may have tended to withdraw early and more frequently due to tolerance reasons.

Some robustness analyses (complete cases analysis, best plausible outcome analysis) were performed in order to show the influence of different methods of handling missing data on the estimation of the product effect. The defined analysis sets were considered appropriate for the objectives of each study. For SANSIKA, Missing data were imputed using the following rules:

- If the patient discontinued before the Month 6 Visit due to lack of tolerance, lack of efficacy or change in dry eye therapy, the patient was considered as a non-responder;
- If the patient discontinued before the Month 6 Visit due to another reason, a last observation carried forward (LOCF) procedure was used carrying forward the Month 3 or Month 1 recording;
- If the patient discontinued before the Month 1 Visit, the patient was considered as a non-responder.

If the evaluation was missing and the patient did not discontinue before the Month 6 Visit:

- An LOCF procedure was used carrying forward the Month 3 or Month 1 recording, or;
- If the Month 1 and 3 recordings were also missing, the patient was considered as a non-responder.

In addition for SICCANOVE, for all analyses except those using LOCF or best plausible case imputation, data from the exit visit of withdrawn patients (recorded in the eCRF as Day 168) were reassigned to the actual withdrawal visit where possible (i.e. if the exit visit was at Day 28 or Day 84). If the exit visit was at an unscheduled visit the data was listed only and not used in any

summary statistics or statistical analyses. For responder analysis, patients without any data under treatment were excluded from the analysis.

Primary hypothesis under investigation

The following primary hypotheses were investigated for each study:

SICCANOVE- To demonstrate the superiority of NOVA22007 (Ciclosporin 0.1%) ophthalmic cationic emulsion versus Vehicle administered once daily in patients with moderate to severe dry eye syndrome after a 6-month treatment period.

SANSIKA-To demonstrate the superiority of NOVA22007 1 mg/mL (CsA) eye drop emulsion over vehicle administered once daily in patients with severe DED after 6 months of treatment.

Statistical test in analysis of primary outcome

SICCANOVE- The co-primary endpoints of this study were:

Objective parameter:

- Change in corneal fluorescein staining from Baseline to Day 168.

Assessments were performed using a 7-point ordinal scale (0, 0.5, 1, 2, 3, 4, 5) (modified Oxford scale).

Subjective parameter:

- Change in global score of ocular discomfort unrelated to study medication instillation, from Baseline to Day 168.

Both primary endpoints were analysed using an ANCOVA model which included treatment with two levels (one for each treatment group), Sjögren status (with two levels: Sjögren, non-Sjögren) and the corresponding Baseline score (defined as the “main model”). The mean change from Baseline was estimated by the least-squares means (LS means). Ninety-five percent confidence intervals (CIs) for the LS means and the LS mean

difference were to be provided. Statistical significance was defined as a *P* value ≤ 0.05 for comparison of LS mean scores.

SANSIKA- The primary efficacy endpoint for this study was defined as the CFS-OSDI composite responder rate at Month 6 (i.e. end of Part 1). A CFS-OSDI responder was defined as a patient satisfying simultaneously the following conditions: Improvement of 2 points or more from Baseline in CFS in the analysis eye (i.e. change in CFS ≤-2), and Improvement by 30% or more from Baseline in OSDI (i.e. % change ≤-30%).

A logistic regression model was carried out with 2 factors, “treatment” and “pooled country”. This model is referred to as the main logistic model. It allowed to test the treatment effect and to obtain point and interval estimates of the odds ratio. In case of a statistically significant treatment effect, a second logistic regression model was carried out with the following 3 factors: “treatment”, “pooled country” and “treatment by pooled country” interaction. This model allowed testing if the difference in responder rate between treatments was homogeneous across countries. The level of significance for the “treatment by pooled country” interaction was set at the 10%.

Power calculation and sample size

SICCANOVE- The sample size calculation was based on a Phase IIa study for the changes at 3 months in corneal fluorescein staining. In this Phase IIa study, the corneal fluorescein staining score was assessed using the Oxford scheme. Based on these data, the mean decrease in Oxford scale from baseline in the Vehicle group was estimated to be 1.0 with a SD of 0.9. The SD was estimated from the pooled SD for the four treatment groups of the Phase IIa study. An additional decrease of 25% in a test treatment group, corresponding to a decrease of 1.25, was considered clinically relevant. The sample size calculation was based upon a two-sided t-test at 5% level of significance. To achieve 80% power of showing a mean difference of 0.25 in change of Oxford scale between two treatment groups, 205 evaluable patients in each treatment group were needed. In order to account for approximately 15% of drop-outs, a total of 482 patients were to be enrolled in the study.

As the co-primary endpoint of this Phase III study was the mean of eight VAS (0-100) symptom scales and the sample size calculation based on the Phase II study results used a global score of ocular discomfort which ranged from 0 to 28, it was decided to perform a confirmatory sample size calculation using co-primary endpoints from the current study prior to unmasking. The sample size calculation above was confirmed using the masked data from the current study and with a small change to the expected difference in CFS (0.25 to 0.35) and an expected difference in VAS of 6 mm.

SANSIKA- The sample size calculation was based on the results of the SICCANOVE study performed in moderate to severe DED patients. In the NVG06C103 study, the rate of CFS-OSDI responders in the targeted population (patients with CFS grade 4 and OSDI ≥23) was 5.6% with the vehicle and 30.8% with NOVA22007 (one drop per day), after 6 months of treatment. The between-group difference corresponded to a ratio of approximately 5.5, meaning that a patient treated with NOVA22007 had approximately a five times greater chance to be a CFS-OSDI responder than a patient treated with the vehicle.

The sample size calculation was performed using a chi-square test with normal approximation, a type I error of 5% (two-sided) and expected CFS-OSDI responder rates of 10% with the vehicle and 28% with NOVA22007. To achieve 90% power, it was estimated that 225 evaluable patients were needed for the main analysis (150 patients with NOVA22007 and 75 patients with the vehicle, according to the allocation ratio 2:1).

Assuming that approximately 10% of patients would not be evaluable for efficacy (and would be excluded from the FAS), a total number of at least 252 patients were to be included in this study (168 with NOVA22007 and 84 with the vehicle).

Supportive analyses of primary outcome

Supportive analyses of the primary efficacy analyses were carried out for both studies:

SICCANOVE- The following secondary analyses were performed to provide evidence of robustness:

1) Sjögren status and Baseline score ANCOVA model as described above (which included treatment with two levels (one for each treatment group), Sjögren status (with two levels: Sjögren, non-Sjögren) and the corresponding Baseline score (defined as the “main model”)) with country effect, and the interaction between treatment group and country effect added (the interaction was removed unless significant at the 10% level, in which case separate models were to be fitted for each country),

2) ANCOVA model as described above using the observed data only,

3) ANCOVA model as described above, with handling of missing data by the best plausible outcome (assigning the worst possible outcome to dropouts for a negative reason and last observation carried forward for dropouts for a reason unrelated to treatment). Assignment of worst possible outcome or last observation carried forward was decided prior to database lock.

SANSIKA- The following secondary analyses were performed:

1) Use of the main logistic model based on the FAS but only considering observed data.

2) Use of the main logistic model based on the FAS, considering the actual treatment received, irrespective of the randomized treatment group.

3) Use of a Cochran-Mantel-Haenszel (CMH) test controlling for pooled country.

Statistical analysis- secondary and other endpoints

Secondary endpoints for both studies were analysed using the following methods:

SICCANOVE- Where appropriate, the main ANCOVA model (treatment with two levels, Sjögren status and Baseline score) was fitted. For parameters analysed by a repeated measures the ANCOVA model was to be fitted to the change from Baseline values at Days 28, 84 and 168 with fixed effect terms for treatment (with two levels: one for each treatment group), Sjögren status (with two levels: Sjögren, non-Sjögren) and Visit (Day 28, 84 or 168) and the corresponding Baseline score as a covariate. The repeated measurements on each patient were to be accounted for in the model by use of a repeated statement and the AR(1) covariance structure was to be used unless evidence showed an alternative structure to better describe the data. If the treatment factor was significant (at the 5% level), contrasts were to be produced in a hierarchical manner to test the difference between products at Day 168 (first step) and if positive, at Day 84 (second step) and Day 28 (third step). The mean change from Baseline was to be estimated by the least-square (LS) means. Ninety-five percent CIs for the LS means and the LS mean difference were to be provided. Normality assumptions were to be assessed using the Shapiro-Wilk test statistic.

SANSIKA- **Part 1**: The responder/non-responder Variables (CFS, OSDI, VAS and CFS-VAS responder rates, and complete corneal clearing rate) were analysed using the main logistic model (with variables “treatment” and “pooled country”). The CFS-OSDI responder rate was presented using frequency distributions at each time point. CFS, OSDI, Global VAS and Lissamine Green change from baseline were analysed using an ANOVA model with the following fixed factors: “treatment”, “visit”, “pooled country” and “treatment by visit” interaction. Schirmer-I, TBUT, NEI-VFQ-25, EQ-5D, Tear film osmolarity and Impression Cytology results were analysed using an ANCOVA model with the following fixed factors: “treatment” and “pooled country”, and the baseline score as covariate, and Shapiro-Wilk test to evaluate normality. Artificial tear use was summarised using descriptive statistics. Investigator Global Evaluation of Efficacy values were regrouped into 0 or 1 (very satisfactory or satisfactory) and 2 or 3 (not very satisfactory or unsatisfactory). Frequency distribution was provided for the original assessment and the regrouped (i.e.

binary) variable. The 2 treatment groups were compared regarding the binary variable using a CMH test controlling for pooled country

Part 2: The responder/non-responder Variables (CFS, OSDI, VAS and CFS-VAS responder rates, and complete corneal clearing rate) were analysed using frequency distributions and exact 95% CI in each treatment group. CFS, OSDI, Global VAS Assessment, Lissamine Green Total Score, Schirmer-I test, TBUT, NEI-VFQ-25, EQ-5D, Impression Cytology, Artificial Tears and Tear Film Osmolarity were analysed using descriptive statistics for change from Baseline values. For the lissamine green total score in the analysis eye, the analysis was repeated without the data of the patients for whom the investigator was not able to perform the examination correctly. The Investigator global evaluation of efficacy at Month 12 was regrouped into 0 or 1 (very satisfactory or satisfactory) and 2 or 3 (not very satisfactory or unsatisfactory). Frequencies were provided for the original assessment and the regrouped (i.e. binary) variable.

Pooled data

SICCANOVE- This study was conducted at 61 clinical sites in six European countries. For the analysis of the co-primary endpoints, the country effect and treatment by country interaction were investigated. Unless the treatment by country interaction was statistically significant, data from all centres/countries were pooled in the reported analyses.

SANSIKA- Due to the large number of centres and the small number of patients per centre, centres were pooled by country. Furthermore, the following pooling of countries was carried out, taking into account geographical and cultural considerations: Belgium and UK regrouped with France, and Czech Republic and Austria with Germany. The analysis of the efficacy variables was performed controlling for pooled country.

Statistical analysis- safety endpoints

SICCANOVE- For the analysis of the quantitative variables recorded at Day 168, the ANCOVA model specified for the analysis of the primary efficacy variable was used. Descriptive summaries were provided for each of the two

treatment groups at each study visit. The number and percentage of subjects reporting treatment-emergent ocular and non-ocular AEs during the study was tabulated by Medical Dictionary for Regulatory Affairs (MedDRA) system, organ, class, and preferred term within each organ by treatment group and by severity.

Best Corrected Distance Visual Acuity (BCDVA), Intraocular Pressure (IOP), Vital Signs and Local Ocular Tolerance (Slit Lamp Examination) were summarized by visit and treatment group using descriptive statistics. CsA concentration data were summarized by visit using frequency distribution of values below the lower limit of detection and values at least equal to the lower limit of detection. Change from Baseline values were used where appropriate.

SANSIKA- All safety analyses were performed on the safety population (SAF for Part 1 and SAF-OPEN for Part 2). The number and percentage of subjects reporting treatment-emergent ocular and non-ocular AEs during the study was tabulated by Medical Dictionary for Regulatory Affairs (MedDRA) system, organ, class, and preferred term within each organ by treatment group and by severity. Post hoc safety analyses of all TEAEs that occurred after the first instillation in the SAF patients who received NOVA22007 during Part 1 were performed at the end of Part 2 to provide a safety overview of the active product over 12 months.

Best Corrected Distance Visual Acuity (BCDVA), Intraocular Pressure (IOP), Vital Signs and Local Ocular Tolerance (Slit Lamp Examination) were summarized by visit and treatment group using descriptive statistics. CsA concentration data were summarized by visit using frequency distribution of values below the lower limit of detection and values at least equal to the lower limit of detection. Change from Baseline (Part 1) or 6-month (Part 2) values were used where appropriate.

Additional Efficacy Analyses

For SICCANOVE, the main ANCOVA model as described above was also to be fitted with the interaction treatment*Sjögren status added to investigate the effect of the two strata of the population. The interaction was tested at the

20% level and removed unless statistically significant. If the interaction was found to be statistically significant, the model was to be fitted to each subgroup separately.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup analysis

SICCANOVE- Post hoc analyses were performed on a set of patients with more severe DED (CFS grade 4) following the finding that the interaction ““treatment by severity of the CFS at Baseline” was statistically significant and guidance from the EMA in a Scientific Advice on 16 Nov 2006 (EMEA/CHMP/SAWP/445808/2006), in which the CHMP suggested the utility of examining the effect of cyclosporin A in the treatment of the most severely affected patients. Following this analysis, post-hoc analyses were also performed in subgroups of patients CFS ≥ 3 and OSDI score ≥ 23 at baseline.

SANSIKA- The following post hoc analyses were performed:

- Analysis of the primary efficacy endpoint (composite CFS-OSDI responder rate) setting the threshold of improvement of CFS at 3 grades instead of 2. This post hoc analysis was carried out to detect a potential treatment effect on patients showing a marked improvement in CFS over 6 months (CFS score at 1 or 0 at the end of Part 1).

- Analysis of the CFS responder rate, setting the threshold of improvement of CFS at 3 grades instead of 2 (i.e. change in CFS ≤-3): Similarly to the post hoc analysis performed on the primary efficacy criterion, this analysis was carried out to detect a potential treatment effect on patients showing a marked improvement in CFS over 6 months.

- Analysis of the primary efficacy endpoint, the composite CFS-OSDI responder rate at Months 1, 3 and 6: The statistical analysis was conducted on observed data, using a generalized linear mixed model. It

was originally planned to only summarize the CFS-OSDI responder rate at Months 1 and 3 using descriptive statistics.

- A post hoc analysis on tear film osmolarity data was performed in the patients with a baseline value higher than 308 mOsms/L (whatever the eye). This was carried out following experts' advice that analysing the worst eye at each visit is more meaningful. In this subgroup of patients, the change in tear film osmolarity from baseline was analysed using an ANCOVA model and taking the worst value of osmolarity between the 2 eyes (eligible or not) at each visit (baseline and Month 6).

- A separate safety analysis was conducted on ocular TEAEs (Part 1 and Part 2).

- Since DED patients with a Sjögren syndrome, a difficult to treat population, represent a subset of the general DED population, further analyses of the composite primary endpoint were performed as part of the prespecific meta-analyses. These analyses were performed with SANSIKA and SICCANOVE data, and based on the 2 well-defined data sets, the all FAS composite primary endpoint (CFS≥2 and of OSDI≥30%) and the severe FAS (CFS=4 and OSDI≥23).

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Patient disposition for the two NOVA22007 trials are presented below.

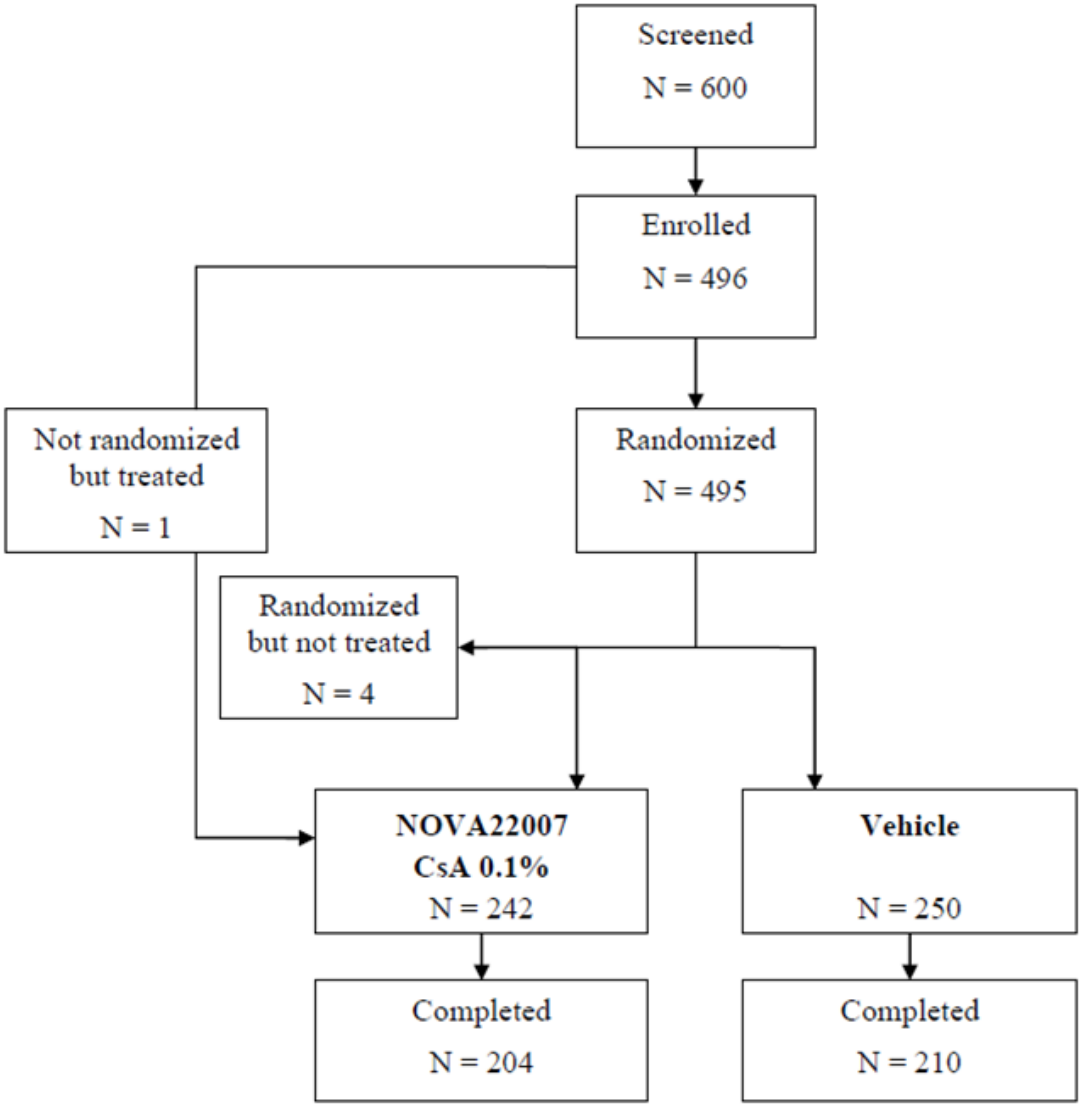
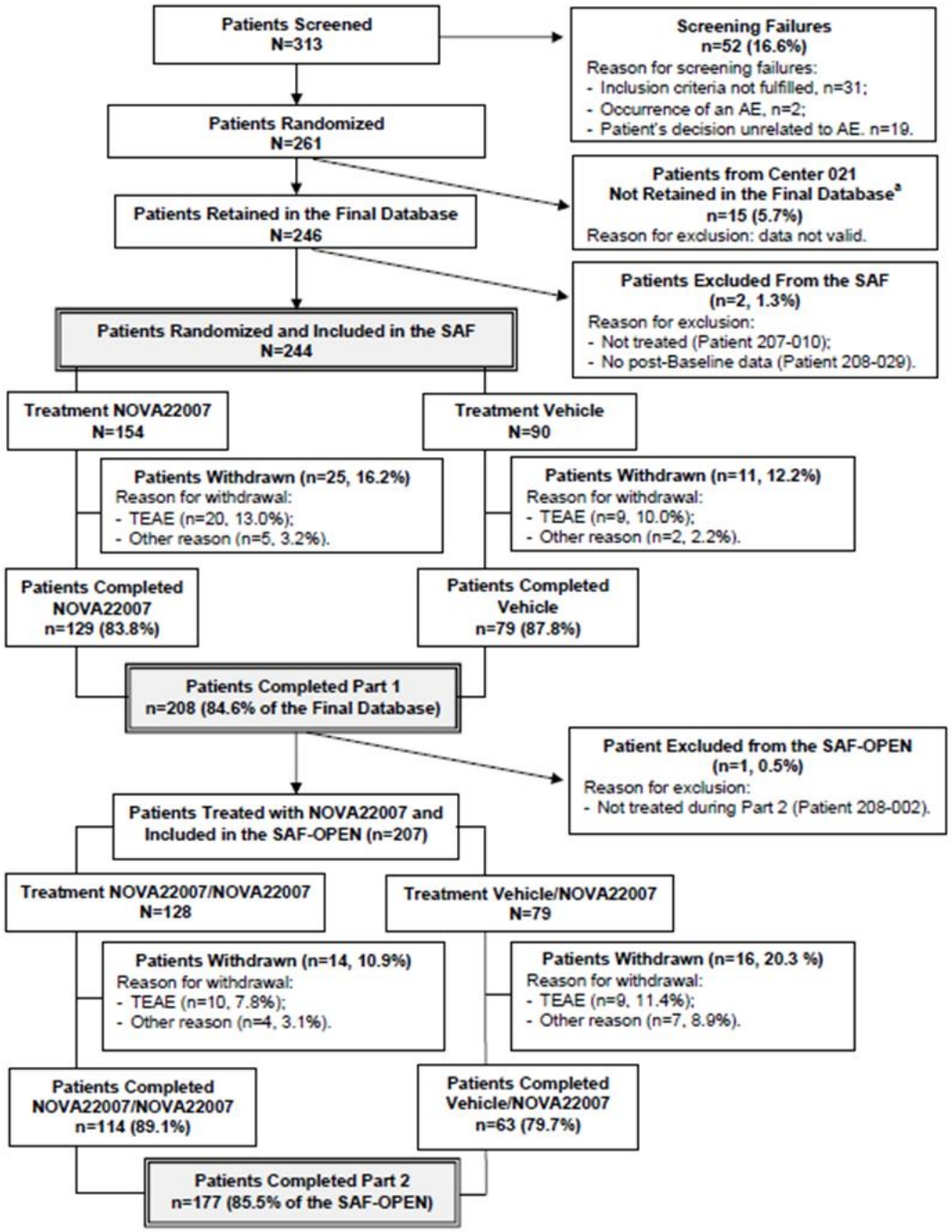


Figure B2 Patient disposition for the SICCANOVE study



AE: adverse event; SAF: Safety Analysis Set; SAF-OPEN: Safety Analysis Set-OPEN; TEAE: treatment-emergent adverse event. A TEAE was defined as an event that started on or after the date of the first study drug dose.
[a] Reason for non-retention was major breach to good clinical practice (GCP) (see Section 11.1).

Figure B3 Patient disposition for the SANSIKA study

6.4 Critical appraisal of relevant RCTs

6.4.1 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B9 Quality assessment results for RCTs

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 randomized patients who received any amount of the study drug, analysed according to their randomised group.	No- full analysis set used which included all randomized patients who received any amount of the study drug, analysed according to their randomised group.

6.5 Results of the relevant RCTs

Primary efficacy endpoints

Corneal fluorescein staining (CFS)

Mean change in CFS from Baseline to Day 168 was a co-primary endpoint for SICCANOVE. For the CFS, the primary analysis (ANCOVA model) was used to estimate a difference of -0.22 (95% CI: -0.39, -0.06) between the treatment

groups. This difference was statistically significant (p=0.009) indicating a significant difference in the change in corneal fluorescein staining from Baseline to Day 168 between the treatment groups in favour of the NOVA22007 group (Table B10). Similar results were obtained from the ordered logistic regression where an odds ratio of 1.53 (95% CI: 1.11, 2.11) was estimated (p=0.010) and from the Van Elteren test (p=0.007).

Table B10 Summary of the primary outcome variables: SICCANOVE and SANSIKA

Phase III SICCANOVE (NVG06C103)				**Phase III SANSIKA (NVG10E117)**			
	NOVA22007 1%	Vehicle	p-value		NOVA22007 1%	Vehicle	p-value
Co-primary endpoint: CFS score: change from baseline at Month 6 – FAS				**Composite primary endpoint: CFS-OSDI response at Month 6 – FAS** **Imputed data (according to the randomized treatment group)**			
n	241	248		N	154	91	
Mean±SD	-1.05± 0.98	-0.82 ± 0.94	p=0.009	Responders, n (%)	44 (28.6)	21 (23.1)	p=0.326
Median	-1.0	-1.0		Non-responders, n (%)	110 (71.4)	70 (76.9)	
Range (min, max)	(-4.0; 2.0)	(-3.0; 1.0)					
Global Score of Ocular Discomfort (VAS)				**Composite primary endpoint: CFS-OSDI response at Month 3 – FAS** **Observed data (according to the randomized treatment group)**			
n	238	245	p= 0.808	N	138	89	NR
Mean±SD	-12.82 ± 18.59	-11.21 ± 19.35		Responders, n (%)	31 (22.6)	12 (13.5)	
Median	-12.50	-8.54		Non-responders, n (%)	107 (77.6)	77 (86.5)	
Range (min, max)	(-62.1; 42.3)	(-74.8; 43.0)		**Composite primary endpoint: CFS-OSDI response at Month 6– FAS** **Observed data (according to the randomized treatment group)**			
				N	131	82	P=0.152

	Responders, n (%)	43 (32.8)	20 (24.4)	
	Non-responders, n (%)	88 (67.2)	62 (75.6)	
	CFS response at Month 6 - FAS			
	N	154	91	
	Responders, n (%)	80 (51.9)	41 (45.1)	p= 0.346
	Non-responders, n (%)	74 (48.1)	50 (54.9)	
	OSDI response at Month 6- FAS			
	N	154	91	
	Responders, n (%)	61 (39.6)	36 (39.6)	P=0.939
	Non-responders, n (%)	93 (60.4)	55 (60.4)	

Supportive analyses of primary endpoint

The primary analyses, CFS score change from baseline and the global score of ocular discomfort in the SICCANOVE study were repeated both without LOCF imputation and with best plausible case imputation. Similar results were shown to the analyses with LOCF imputation for the FAS (p=0.003 for ‘without LOCF imputation’ and p=0.010 for ‘best plausible case imputation’).

Subgroup analyses

For the SICCANOVE study, there was a significant treatment by country interaction (p=0.020) in the FAS indicating that the effect of treatment differed between countries. In most countries (France, Germany, Italy and Spain) the estimated treatment difference between groups was in favour of NOVA22007, while it was (not significantly) in favour of Vehicle in two countries (Czech Republic and UK) The results observed in Czech Republic and UK needed to be further explained and therefore some additional post-hoc analyses were performed to understand this finding The following paragraphs describe differences and potential explanations for the observed country differences.

With regards to UK, a high number of patients had blepharitis (19 of 30 patients [63.3%] enrolled in this country), among them 8 in the NOVA22007 group. In the rest of the population, only 10/462 patients (2.2%) enrolled had a blepharitis. It is possible that the high number of patients with blepharitis in the UK may explain the lesser efficacy of NOVA22007 in this country, since blepharitis has a different patholophysiology to keratitis.

For the Czech Republic, .a plausible explanation for the reduced effect is that patients in this country have been found to be having less severe dry eye syndrome at Baseline. Fewer patients were enrolled with grade 4 on the modified Oxford scale compared to other countries (Table B11). Thus, the interaction “treatment by severity of the corneal fluorescein staining at Baseline” was tested in the main model of analysis and was statistically significant with a p-value = 0.011. This finding led to a further subgroup analysis in patients with more severe score of corneal fluorescein staining at inclusion (Table B12).

These post hoc analyses were performed on a subset of patients with severe dry eye disease, defined as having a grade 4 at baseline. This severe patient population represented 17% of the overall SICCANOVE population at baseline (n=85). In the Full Analysis Set, the mean change in corneal fluorescein staining from Baseline to Day 168 was -1.47 (NOVA22007) and -0.69 (Vehicle). A statistically significant treatment effect in favour of NOVA22007 was shown using an ANCOVA model (p=0.002).

The results of these post-hoc analyses showed that the efficacy of NOVA22007 was greater in the most severe cases (grade 4 on the modified Oxford scale) than in the overall study population. This patient group represents a challenging subgroup of eyes at risk for irreversible damage to the ocular surface, particularly the cornea. These analyses provide a plausible explanation for the clinical findings observed in the Czech Republic. Specifically, in Czech Republic fewer patients were enrolled with grade 4 corneal staining on the modified Oxford scale compared to patients enrolled in other countries. Thus, the lower efficacy observed for Czech Republic may be an effect of the related severity of corneal staining rather than country.

Table B11 Relationship Between Country and Corneal Fluorescein Staining at Baseline - Worse Eligible Eye (Full Analysis Set)

CFS at Baseline	Czech Rep	France	Italy	Spain	Germany	UK
	N=95	N=89	N=117	N=85	N=73	N=30
Grade 2	41.1%	31.5%	36.8%	29.4%	43.8%	36.7%
Grade 3	53.7%	41.6%	50.4%	43.5%	38.4%	46.7%
Grade 4	5.3%	27.0%	12.8%	27.1%	17.8%	16.7%
Chi-square						
P value =0.005						

Patient 041 003 (France) with a score of 5 has been pooled with patients with a score of 4

Table B12 Analysis of Corneal Fluorescein Staining by Severity of Corneal Fluorescein Staining At Baseline - Worse Eligible Eye (Full Analysis Set)

CFS at Baseline	Improvement in CFS (LS mean)			
	NOVA22007 CsA 0.1%	Vehicle	Delta	p-value
Grade 3 and 4	1.17	0.86	0.32	0.005
Grade 4	1.47	0.69	0.77	0.002

Patient 041 003 (France) with a score of 5 has been pooled with patients with a score of 4

In the SANSIKA study, a post hoc analysis was carried out using those patients who had at least 3 grades improvement on the CFS at month 6 (Table B13). In the FAS and based on imputed data (according to the randomized treatment group), the CFS (at least 3 grades improvement) responder rate was statistically significantly higher (p=0.002) with NOVA22007 than with vehicle. The chance to be a CFS responder was approximately 3 times higher with NOVA22007 than with vehicle (odds ratio: 3.0, 95% CI [1.5;6.3]).

These results were confirmed when considering observed data. A total of 47 patients (35.6%) assigned to NOVA22007 and 12 patients (14.5%) assigned to vehicle showed a positive CFS response at Month 6. The difference between groups was statistically significant (p=0.001). Based on observed data, the chance to be a responder was approximately 3.3 times higher with NOVA22007 than with vehicle (odds ratio: 3.3, 95% CI [1.6;7.0]).

Table B13 CFS (at Least 3 Grades Improvement) Response at Month 6 (FAS)

	NOVA22007	Vehicle	p-value^
Imputed data (according to the randomized treatment group)			
N	154	91	
Responders, n (%)*	48 (31.2)	12 (13.2)	p=0.002
Non-responders, n (%)	106 (68.8)	79 (86.8)	
Observed data			
N[ł]	132	83	
Responders, n (%)*	47 (35.6)	12 (14.5)	p=0.001
Non-responders, n (%)	85 (64.4)	71 (85.5)	

*CFS (at least 3 grades improvement) responder: improvement of 3 points or more from Baseline in CFS in the analysis eye (i.e. change in CFS ≤ -3).

^ p-value for treatment effect in the logistic regression model.

ł Total sample size for this analysis was 215 (132+83 patients), i.e. there were 30 missing data.

CFS-OSDI response in patients with Sjögren syndrome

In the Sjögren ALL FAS, the rate of responders was 19.2% for NOVA22007 and 11.6% for vehicle giving an Odd-Ratio of 1.773 [0.893; 3.657] showing a particular interest of NOVA22007 in these Sjögren patients particularly difficult to treat/improve. Therefore this result reinforces the interest of NOVA22007 in severe DED patients (CFS grade 4). Results are illustrated further in Table B14 and with the Forest plots below (Figure B4).

Table B14 CFS/OSDI response at Month 6 (imputed data) in the Sjögren set in ALL FAS

		IKERVIS (n=395)		Vehicle (n=339)	
SANSIKA		**n**	**%**	**n**	**%**
	Responders	12	20.7	10	11.5
	Non-responders	46	79.3	77	88.5
	Total	58	100	87	100
SICCANOVE		**n**	**%**	**n**	**%**
	Responders	16	18.2	10	11.5
	Non-responders	72	81.8	77	88.5
	Total	88	100	87	100
SANSIKA + SICCANOVE		**n**	**%**	**n**	**%**
	Responders	28	19.2	14	11.6
	Non-responders	118	80.8	107	88.4
	Total	146	100	121	100

Logistic regression with Treatment Study Interaction

p-value (Treatment)= 0.113

p-value (Study)= 0.796

p-value (Pooled country)= 0.926

p-value (Treatment Study interaction)= 0.794

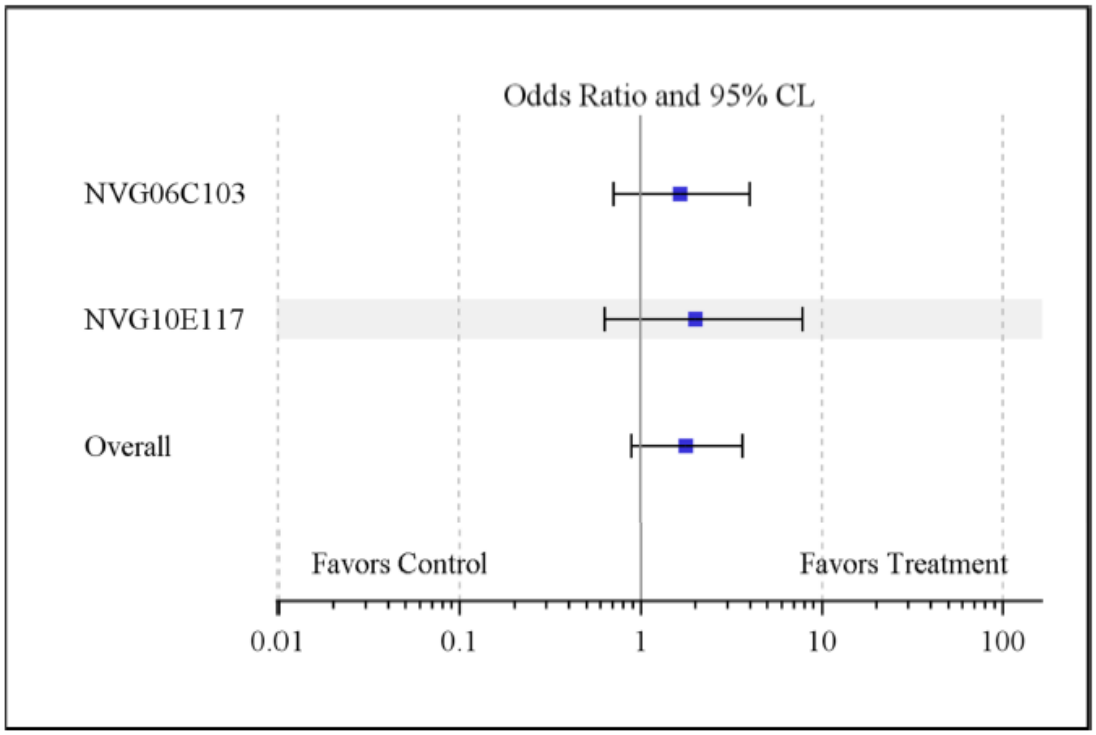


Figure B4 Meta-analyses – CFS/OSDI response at Month 6 in the Sjögren set in ALL-FAS

There was no difference observed when analysing the Sjögren severe set in the severe FAS data as detailed in Table B15 below.

Table B15 CFS/OSDI response at Month 6 (imputed data) in the Sjögren set in Severe FAS

		IKERVIS (n=193)		**Vehicle (n=126)**	
SANSIKA		**n**	**%**	**n**	**%**
	Responders	12	20.7	4	11.8
	Non-responders	46	79.3	30	88.2
	Total	58	100	34	100
SICCANOVE		**n**	**%**	**n**	**%**
	Responders	6	31.6	1	5.3
	Non-responders	13	68.4	18	94.7
	Total	19	100	19	100
SANSIKA + SICCANOVE		**n**	**%**	**n**	**%**
	Responders	18	23.4	5	9.4
	Non-responders	59	76.6	48	90.6
	Total	77	100	53	100

Logistic regression with Treatment Study Interaction

p-value (Treatment)= 0.028

p-value (Study)= 0.987

p-value (Pooled country)= 0.650

p-value (Treatment Study interaction)= 0.288

Related secondary outcome analyses

In the SICCANOVE study, CFS was measured at days 28 and 84 in addition to day 168 (Primary endpoint). For the Full Analysis Set, the mean change in corneal fluorescein staining score from Baseline to Day 28 was -0.77 and -0.52 for the NOVA22007 and Vehicle groups, respectively. A statistically significant treatment effect in favour of NOVA22007 was shown (p=0.002). At Day 84, the mean change from Baseline was -0.92 and -0.70 for the NOVA22007 and Vehicle groups, respectively; a statistically significant treatment effect in favour of NOVA22007 (p=0.030). These findings indicate that the improvement in the objective sign is present as early as 1 month and also after 3 months of treatment.

The percentage of complete responders (score of zero on the modified Oxford scale) was also measured for the FAS in the SICCANOVE study. The percentage increased in both treatment groups during the study. The percentage of complete responders at Day 28 (3.32% vs. 2.42%), Day 84 (7.05% vs. 3.63%) and Day 168 (8.30% vs. 5.24%) for the NOVA22007 and Vehicle groups, respectively, was comparable between the treatment groups and at Day 168 the difference was not statistically significant (p=0.175).

In the SANSIKA study, CFS responder rate (improvement of ≥2 points from Baseline in CFS in the analysis eye) at Month 6 was found to have no statistically significant difference between NOVA22007 and vehicle (p=0.346). Complete corneal clearing, i.e. CFS score going from 4 down to 0, was achieved within 6 months in 6.5% of patients assigned to NOVA22007 and 4.4% of patients assigned with vehicle. The difference between treatment groups was not statistically different.

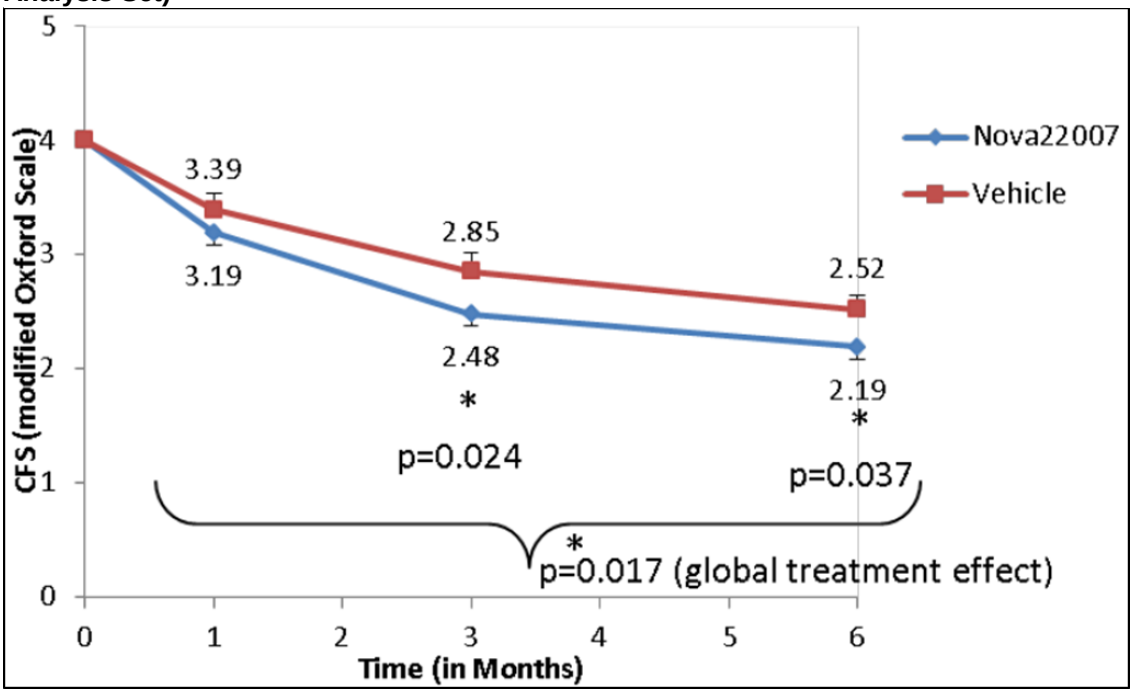
For Part 2 of the SANSIKA study (6-12 months), the CFS responder rate at Month 12 was higher in the NOVA22007/NOVA22007 group (65.6%, 95% CI [56.7;73.8]) than in the vehicle/NOVA22007 group (54.4%, 95% CI

[42.8;65.7]). There was also an increase in the responder rate of the NOVA22007/NOVA22007 group from month 6 to months 12, the CFS responder rate increased from 51.9% to 65.6% (+13.7 points), the OSDI responder rate from 39.6% to 52.3% (+12.7 points), the VAS responder rate from 31.2% to 53.9% (+22.7 points) and the CFS-VAS responder rate from 22.7% to 42.2% (+19.5 points).

Complete corneal clearing, i.e. CFS scored 0, was achieved within 12 months in a similar proportion of patients in the NOVA22007/NOVA22007 group (12.5%, 95% CI [7.3;19.5]) and in the vehicle/NOVA22007 group (11.4%, 95% CI [5.3;20.5]). In the patients treated with NOVA22007 for 12 months (NOVA22007/NOVA22007 group), complete corneal clearing rate was approximately 2 times higher at Month 12 (12.5%) than it was at Month 6 (6.5%) in the NOVA22007 group. In the patients treated with vehicle for 6 months (vehicle group), then NOVA22007 for 6 months (vehicle/NOVA22007 group), complete corneal clearing rate was lower with vehicle (4.4% at Month 6) than with NOVA22007 (11.4% at Month 12, i.e. +7 points compared to Month 6).

CFS score change from Baseline was also analysed as a secondary outcome in the SANSIKA study at months 1, 3 and 6 (Figure B3). There was a statistically significant decrease (i.e. improvement) in CFS score over time ($p<0.001$) in the FAS patients. Over the 6-month treatment period, a global effect of treatment in favour of NOVA22007 over vehicle regarding the change in CFS score from baseline was observed ($p=0.017$). The decrease in CFS score from Baseline was greater with NOVA22007 than with vehicle at each time point, reaching statistical significance at Month 6 ($p=0.037$), and as early as Month 3 ($p=0.024$). At Month 3, the adjusted mean change in CFS score from Baseline was -1.51 with NOVA22007 and -1.13 with vehicle. At the end of Part 1 (Month 6 Visit), the adjusted mean change in CFS score from baseline was -1.76 with NOVA22007 and -1.42 with vehicle.

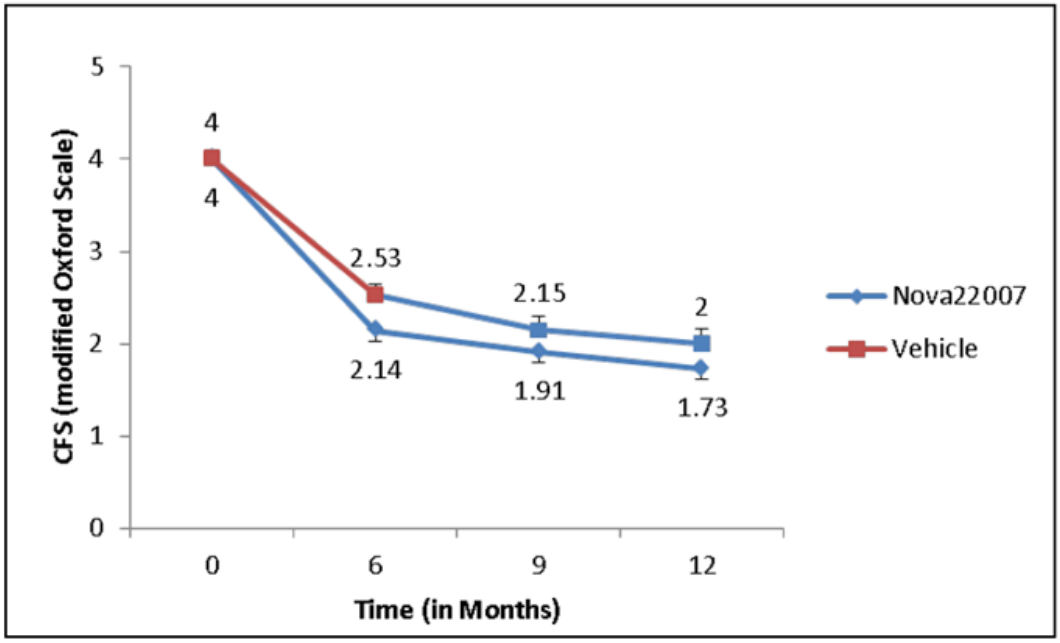
Figure B5 Mean CFS Scores from Baseline to Month 6 in the Analysis Eye –Part 1 (Full Analysis Set)



The global effect of treatment on the change in CFS score from Baseline in favour of NOVA22007 was also found when adjusting for the average number of artificial tears used per day (p=0.021).

This analysis of CFS score change from Baseline was also repeated at Month 12 following the open-label study period (Figure B4). Mean CFS score decreased (i.e. improved) steadily between baseline and Month 12 in the NOVA22007/NOVA22007 group (-2.3) and the vehicle/NOVA22007 group (-2.0). The improvement was greater during the first 6 months (-1.86 and -1.47 in the NOVA22007/NOVA22007 group and the vehicle/NOVA22007 group, respectively) than during the last 6 months (-0.37 and -0.53, respectively).

Figure B6 Mean CFS Scores from Baseline to Month 12 in the Analysis Eye –Part 1 and 2 (FAS-OPEN)



Sample size at Baseline, Month 6, 9 and 12: 128, 128, 127 and 115 with NOVA22007, and 79, 79, 75 and 65 in vehicle.

Clinical significance of CFS results

In the SICCANOVE study, a statistically significant treatment effect in favour of NOVA22007 in CFS was shown using an ANCOVA model (p=0.009). The improvement in this objective endpoint indicates a therapeutic benefit in comparison to Vehicle treatment. These findings were supported by a non-parametric analysis and in the predefined robustness analyses.

Ocular discomfort

In the SICCANOVE study, for the Global VAS score (FAS population), using an ANCOVA model, which included treatment, Sjögren status and baseline score, the estimated difference was -0.39 (95% CI: -3.54, 2.76). No statistically significant treatment effect was shown (p=0.808) and the second primary objective was not met (Table B10). The treatment by country interaction was not statistically significant (p=0.455) so results were not split by country. The treatment by Sjögren status interaction was not statistically significant (p=0.344) so results were not split by Sjögren status.

Supportive analyses of primary endpoint

For the SICCANOVE study, the primary analyses were repeated without LOCF imputation and using best plausible case imputation. Similar results were shown to the FAS populations (P=0.623 without LOCF imputation and P=0.944 using best possible case imputation).

Related secondary outcome analyses

For the SICCANOVE study, the percentage of responders (according to the VAS) was also analysed. For the Full Analysis Set, the percentage of responders (defined as a percentage decrease from baseline of at least 25% in VAS score) at Day 28 (40.66% vs. 39.11%), Day 84 (48.13% vs. 45.97%) and Day 168 (50.21% vs. 41.94%) was statistically significantly different between treatment groups in favour of NOVA22007 (p=0.048) at Day 168. This indicates that even though the estimated mean difference in global VAS score between the treatment groups was small, more patients (almost 10% more) in the NOVA22007 group did respond according to this predefined definition.

In addition, for the SICCANOVE study, each individual symptom on the VAS was assessed as secondary outcome. Results were as follows for the FAS:

- Itching: The mean change in “itching‟ ocular discomfort score from Baseline to Day 168 was -12.59 (NOVA22007) and -11.55 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.390).

- Foreign body sensation: The mean change in “foreign body sensation‟ ocular discomfort score from Baseline to Day 168 was -17.28 (NOVA22007) and -14.46 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.510).

- Blurred vision: The mean change in “blurred vision‟ ocular discomfort score from Baseline to Day 168 was -11.24 (NOVA22007) and -10.02 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.877).

- Eye dryness: The mean change in “eye dryness‟ ocular discomfort score from Baseline to Day 168 was -26.84 (NOVA22007and -19.90 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.114).

- Photophobia: The mean change in “photophobia‟ ocular discomfort score from Baseline to Day 168 was -11.29 (NOVA22007) and -11.69 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.296).

- Pain: The mean change in “pain‟ ocular discomfort score from Baseline to Day 168 was -10.38 (NOVA22007) and -9.07 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.201).

- Sticky feeling: The mean change in “sticky feeling‟ ocular discomfort score from Baseline to Day 168 was -12.44 (NOVA22007) and -8.67 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.453).

- Global score: The mean change in “global‟ ocular discomfort score from Baseline to Day 168 was -14.40 (NOVA22007) and -12.16 (Vehicle). A repeated measures ANCOVA indicated no statistically significant overall treatment effect (p=0.787)

For the SANSIKA study, responder rate (defined as improvement by ≥30% from Baseline in global VAS assessment in the analysis eye) was measured as a secondary outcome. There were no statistically significant differences in VAS responder rate between groups (P= 0.302) at month 6. Responder rates between groups were also very similar at Month 12.

In addition, change in global VAS score was measured as a secondary outcome in the SANSIKA study. There was a statistically significant decrease (i.e. improvement) in the global VAS assessment score of ocular discomfort over time in the FAS patients (p=0.010), with no statistically significant difference between treatment groups. The absence of a difference between

NOVA22007 and vehicle regarding the change in the global VAS assessment score from baseline was also found when adjusting for the average number of artificial tears used per day. For the open-label study (Months 6-12), Median global VAS assessment scores decreased (i.e. improved) steadily between baseline and Month 12 in the NOVA22007/NOVA22007 group (-21.6) and the vehicle/NOVA22007 group (-20.7). This improvement tended to be greater during the first 6 months (-11.5 and -9.9 mm in the NOVA22007/NOVA22007 group and the vehicle/NOVA22007 group, respectively) than during the last 6 months (-5.7 and -6.5 mm, respectively). The analysis of the 8 individual VAS scores, each assessing a specific symptom of ocular discomfort, showed that all 8 symptoms improved over the 12-month period.

CFS-OSDI

For SANSIKA only, the primary endpoint was the CFS-OSDI responder rate at month 6. Based on imputed data (according to the randomized treatment group), the CFS-OSDI responder rate was slightly higher in the NOVA22007 group (44 patients, 28.6%) than in the vehicle group (21 patients, 23.1%); however, the slight difference in favour of the NOVA22007 group (+5.5 points) was not statistically significant.

Supportive analyses of primary endpoint

In SANSIKA, when running the primary analysis using imputed data according to the actual treatment received, similar CFS-OSDI responder rates were found (45 patients, 29.0%, with NOVA22007, versus 20 patients, 22.2%, with vehicle). The difference in favor of the NOVA22007 group increased slightly (+6.8 points) but remained not statistically significant.

In addition, when considering observed data (i.e. missing data not imputed) at 3 months, the CFS-OSDI responder rates were slightly higher in both groups (31 patients, 22.6%, with NOVA22007, versus 12 patients, 13.5%, with vehicle). The difference in favor of the NOVA22007 group was not statistically significant at 3 months. Similarly, the CFS-OSDI responder rates were slightly higher in both groups at 6 months (43 patients, 32.8%, with NOVA22007, versus 20 patients, 24.4%, with vehicle). The difference in favor of the

NOVA22007 group increased further (+8.4 points) but remained not statistically significant. Importantly, this analysis did not include patients who were discontinued prematurely due to lack of efficacy or to a TEAE and who were considered as non-responders when imputing missing data.

For SANSIKA, the responder rate at Month 6 using a more stringent definition (at least 3 grades improvement for CFS) was analysed post-hoc for the FAS (Table B16). The CFS-OSDI responder rate was statistically significantly higher (p=0.016) with NOVA22007 than with vehicle at Month 6. From a clinical point of view, this difference corresponds to a 3-time higher chance to be a responder with NOVA22007 than with vehicle after 6 months of treatment (odds ratio: 2.9, 95% CI [1.3;7.7]). These results were confirmed when considering observed data. The responder rate in the NOVA22007 group was higher than in the vehicle group. The difference between groups was statistically significant (p=0.012). Based on observed data, the chance to be a responder was approximately 3 times higher with NOVA22007 than with vehicle (odds ratio: 3.2, 95% CI [1.4;8.3]).

Table B16 CFS (at Least 3 Grades Improvement)-OSDI Response at Month 6 (FAS)

	NOVA22007	Vehicle	p-value^
Imputed data (according to the randomized treatment group)			
N	154	91	
Responders, n (%)*	29 (18.8)	7 (7.7)	p=0.016
Non-responders, n (%)	125 (81.2)	84 (92.3)	
Observed data			
N'	131	82	
Responders, n (%)*	28 (21.4)	7 (8.5)	p=0.012
Non-responders, n (%)	103 (78.6)	75 (91.5)	

*CFS (at least 3 grades improvement)-OSDI responder: improvement of 3 points or more from Baseline in CFS in the analysis eye (i.e. change in CFS □-2) and improvement by 30% or more from Baseline in OSDI (i.e. % change ≤-30%).

^p-value for treatment effect in the logistic regression model.

'Total sample size for this analysis was 213 (131+82 patients), i.e. there were 32 missing data.

Subgroup analyses

In SICCANOVE (prior to the development of the CFS-OSDI SANSIKA endpoint), Post-hoc analyses were performed on a subset of patients with corneal fluorescein staining score ≥ 3 (excluding the less severe patients, i.e. CFS grade 2) and OSDI score ≥ 23 (excluding patients with mild symptoms) at Baseline. This population represented 50% of the overall study population (n=246). The post hoc analyses showed the superiority of NOVA22007 over Vehicle in this population. Statistically significant between-group differences in favour of NOVA22007 were observed in the following clinical parameters in the FAS population: Percentage of responders on corneal fluorescein staining and percentage of co-responders on both a sign (improvement in CFS) and a symptom (improvement in OSDI score). The percentage of co-responders on both signs (defined as patients with at least 2 grades improvement in corneal fluorescein staining on the modified Oxford scale) and symptom (defined as patients with at least 30% improvement in OSDI) was 19.53% vs. 10.17% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.049).

In SANSIKA, there was no statistically significant difference in CFS-OSDI responder rate between pooled countries (see Section 14.2.1, Table 14.2.1.1.2). However, there was a tendency for higher CFS-OSDI responder rate with vehicle in Italy (12 patients, 41.4%) than in other countries (rates ranging from 10.5% to 20.0%).

Related secondary outcome analyses

For SANSIKA, The primary efficacy variable, which was the composite CFS-OSDI response (i.e. a ≤2 point improvement in CFS and a ≥30% improvement in OSDI) from baseline) was examined at Months 1, 3 and 6, and analysed through a generalised mixed model (Table B17 and Figure B7). Based on observed data, the CFS-OSDI responder rate increased over time in the FAS patients regardless of treatment group (p<0.0001). When considering all study visits, CFS-OSDI responder rate was statistically significantly higher with NOVA22007 than with vehicle (p=0.043). In a sensitivity purpose, the same analysis was also performed with imputed data. Results of this analysis gave

a similar trend, but without reaching the statistical significance (FAS, p=0.075).

Table B17 CFS-OSDI Response Over Time – Part 1 (FAS)

	NOVA22007	**Vehicle**	**Generalized linear mixed model^**	
	N=154	**N=91**		
			Effect	**p-value**
Month 1	N=149	N=87	Treatment (global)	p=0.043
Responders, n (%)[1]	14 (9.4)	4 (4.6)	Pooled country	p=0.121
Non-responders, n (%)	135 (90.6)	83 (95.4)	Visit	p<0.0001
Month 3	N=138	N=89	Treatment*Visit	p=0.752
Responders, n (%)[1]	31 (22.5)	12 (13.5)		
Non-responders, n (%)	107 (77.5)	77 (86.5)		
Month 6	N=131	N=82		
Responders, n (%)[1]	43 (32.8)	20 (24.4)		
Non-responders, n (%)	88 (67.2)	62 (75.6)		

[1]CFS-OSDI responder: improvement of 2 points or more from Baseline in CFS in the analysis eye (i.e. change in CFS ≤-2) and improvement by 30% or more from Baseline in OSDI (i.e. % change ≤-30%).

^The statistical analysis was conducted on observed data (according to treatment as randomized during Part 1),using a generalized linear mixed model.

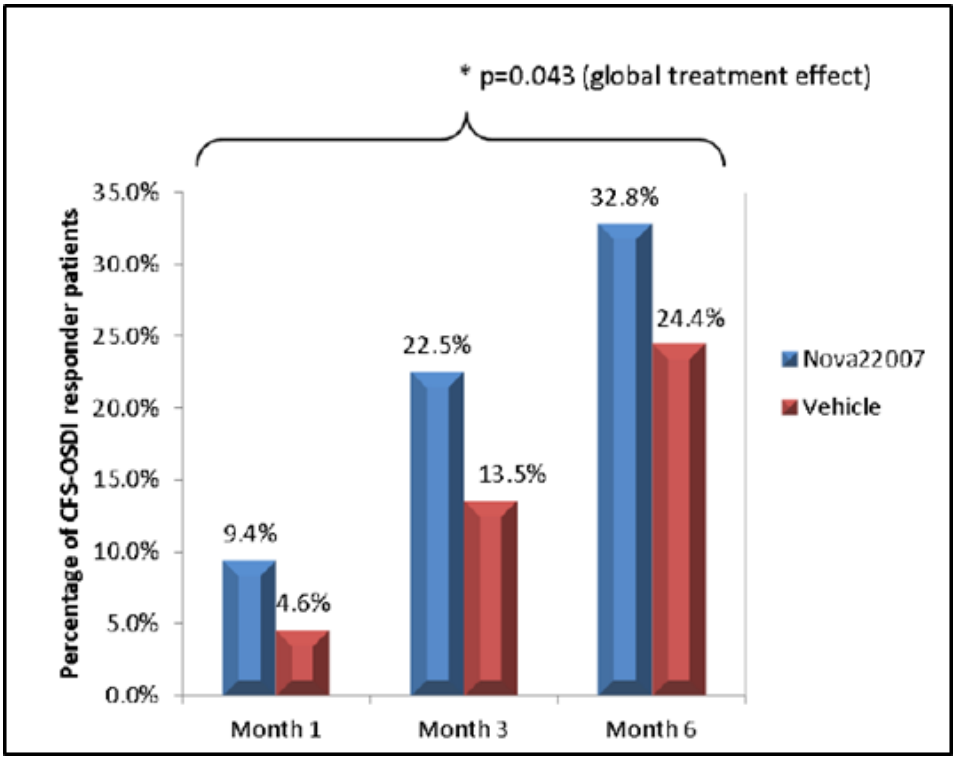


Figure B7 Percentage of Composite CFS-OSDI Responders Over Time – Part 1 (FAS)

The CFS-OSDI responder rate was also analysed in Part 2 of SANSIKA (open-label study); the CFS-OSDI responder rates were similar in both treatment groups, at Months 9 and 12. Between Month 9 and Month 12, in the NOVA22007/NOVA22007 group, the CFS-OSDI responder rate increased by 5.5 points, from 33.6% (95% CI [25.5;42.5]) to 39.1% (95% CI [30.6;48.1]). Over the same period, the CFS-OSDI responder rate increased by 2.6 points in the vehicle/NOVA22007 group, from 35.4% (95% CI [25.0;47.0]) to 38.0% (95% CI [27.3;49.6]). Together with the CFS-OSDI responder rates observed at Months 1, 3 and 6 (Table B17), these results showed an increase in the CFS-OSDI responder rate over the 12-month period in both groups. In the NOVA22007 group, the CFS-OSDI responder rate increased markedly during the first 6 months (32.8% at Month 6). In the NOVA22007/NOVA22007 group (patients who received NOV22007 for 12 months), the rate increased further during the last 6 months but less rapidly (39.1% at Month 12, i.e. +6.3 points) compared to Month 6.

In the vehicle group, the CFS-OSDI responder rate increased during the first 6 months (24.4% at Month 6). In the vehicle/NOVA22007 group (patients who

received the vehicle and were switched after 6 months to NOVA22007), the rate increased further and quite rapidly (catching up with the NOVA2007/NOVA22007 group) during the last 6 months, when patients were treated with NOVA22007 (38.0% at Month 12, i.e. +13.6 points compared to Month 6).

Secondary efficacy endpoints

Lissamine Green Staining

In the SICCANOVE study, the overall score at Baseline for lissamine green staining of the interpalpebral conjunctiva was comparable between treatment groups for the FAS (5.68 vs. 5.71). The changes in score from Baseline were slightly greater for the NOVA22007 group at all timepoints: Day 28 (-1.52 vs. -1.30), Day 84 (-2.12 vs. -1.74) and Day 168 (-2.37 vs. -2.18).

At Day 168, an ANCOVA (with treatment group and Sjögren status as factors and Baseline score as a covariate) showed an estimated difference of -0.22 (95% CI: -0.59, 0.15) with a p-value of 0.250, indicating no statistically significant difference between the treatment groups. However, a repeated measures ANCOVA (with treatment group, visit, treatment by visit interaction and Sjögren status as factors and Baseline score as a covariate) showed a statistically significant overall treatment effect in favour of the NOVA22007group (p=0.048), supporting the results shown on the co-primary endpoint (global score of corneal fluorescein staining).

Post hoc analyses were performed during SICCANOVE on a subset of patients with severe dry eye (CFS grade 4 at baseline). Mean change in lissamine green staining of the interpalpebral conjunctiva from Baseline to Day 168 was -2.31 (NOVA22007) and -0.73 (Vehicle). A statistically significant treatment effect in favour of NOVA22007 was shown using an ANCOVA model (n= 85, p=0.003).

During the SANSIKA study, some Investigators declared that they were not able to perform the examination correctly. Therefore, during the blind review meeting, it was decided to perform a second analysis of the lissamine green total score, excluding patients for whom a problem was reported. Total n for those included can be found in Table B18.

Mean (±SD) lissamine green total score at baseline was similar in both treatment groups (4.5±2.1 with NOVA22007 and 4.6±2.1 with vehicle). There was a statistically significant decrease in the lissamine green total score over

time in the FAS patients ($p<0.001$), with no statistically significant difference between treatment groups. At the Month 6 Visit, the adjusted mean change in the lissamine green total score from Baseline was -1.7 with NOVA22007 and -1.4 with vehicle.

When repeated at Month 12 following Part 2 of the SANSIKA study, mean lissamine green total score decreased (i.e. improved) between baseline and Month 6, then remained stable until Month 12, in both treatment groups. The change over 12 months was -1.8 in the NOVA22007/NOVA22007 group and -1.7 in the vehicle/NOVA22007 group.

Table B18 Lissamine Green Total Scores Over Time and Absolute Change from Baseline (FAS – Subgroup of Patients)

	NOVA22007 N=154	Vehicle N=91	ANOVA^	
			Effect	**p-value**
Baseline	**N=34**	**N=79**	Treatment (global)	p=0.989
Mean±SD	4.46±2.10	4.59±2.15	Pooled country	p=0.340
Median	4.00	5.00	Visit	p<0.001
Range (min;max)	(0.0;9.0)	(0.0;9.0)	Treatment*Visit	p=0.313
Month 1	**N=128**	**N=76**		
Mean±SD	3.65±2.22	3.59±2.21		
Median	3.00	3.00		
Range (min;max)	(0.0;9.0)	(0.0;8.0)		
Change from Baseline at Month 1	**N=128**	**N=76**		
Mean±SD	-0.84±1.83	-0.97±2.33	Contrast for	p=0.690
Adjusted mean (95% CI)^	-0.818 (-1.185;-0.451)	-0.935 (-1.416;-0.454)	Treatment (Month 1)	
Median	-1.00	-1.00		
Range (min;max)	(-7.0;6.0)	(-8.0;6.0)		
Month 3	**N=122**	**N=77**		
Mean±SD	3.08±2.24	3.13±2.07		
Median	3.00	3.00		
Range (min;max)	(0.0;9.0)	(0.0;8.0)		
Change from Baseline at Month 3	**N=122**	**N=77**		
Mean±SD	-1.33±2.18	-1.48±2.29	Contrast for	p=0.681
Adjusted mean (95% CI)^	-1.321 (-1.725;-0.917)	-1.453 (-1.972;-0.934)	Treatment (Month 3)	
Median	-1.00	-1.00		
Range (min;max)	(-7.0;6.0)	(-9.0;6.0)		

	NOVA22007 N=154	Vehicle N=91	ANOVA^	
			Effect	**p-value**
Month 6	**N=114**	**N=71**		
Mean±SD	2.68±2.20	3.13±2.08		
Median	2.00	3.00		
Range (min;max)	(0.0;8.0)	(0.0;9.0)		
Change from Baseline at Month 6	**N=114**	**N=71**		
Mean±SD	-1.74±2.09	-1.52±2.16	Contrast for Treatment (Month 6)	p=0.411
Adjusted mean (95% CI)^	-1.665 (-2.062;-1.267)	-1.405 (-1.917;-0.893)		
Median	-2.00	-1.00		
Range (min;max)	(-6.0;4.0)	(-9.0;5.0)		

^Adjusted means were obtained using a repeated measure analysis of variance (ANOVA) model with the following fixed factors: “treatment”, “visit”, “pooled country” and “treatment by visit” interaction. The treatment effects at Month 6, 3 and 1 are referred to as “contrast for treatment” effect in the table. Please refer to Section 9.7.7.1 for more details on the statistics.

Tear Break up Time

In the SICCANOVE study, for the Full Analysis Set, both treatment groups showed an improvement in TBUT between Baseline and Day 168 (1.17 s [NOVA22007]; 1.13 s [Vehicle]). However, there was no statistically significant treatment effect at Day 28, 84 or 168.

For SANSIKA, Mean (±SD) TBUT at baseline was similar in both treatment groups (3.3±1.6 s with NOVA22007 and 3.5±1.7 s with vehicle). There was an increase (i.e. improvement) in TBUT over time in both treatment groups. At Month 6, the mean change in TBUT from baseline was +0.75 s with NOVA22007 and +0.30 s with vehicle. The difference between treatment groups was not statistically significant.

During Part 2 of SANSIKA (open-label), Mean TBUT increased between Baseline and Month 12 in the NOVA22007/NOVA22007 group (+0.90 s) and

the vehicle/NOVA22007 group (+0.33 s). The improvement mainly occurred during the first 6 months (+0.74 and +0.33 s in the NOVA22007/NOVA22007 group and the vehicle/NOVA22007 group, respectively), as TBUT remained relatively stable during the last 6 months (+0.15 and +0.04 s, respectively).

Artificial tear usage

In the SICCANOVE study, for the Full Analysis Set, the average number of times per day artificial tears were used preceding Baseline (i.e. since Screening) was 5.6 (NOVA22007) and 5.4 (Vehicle). Mean number of instillations of artificial tears was slightly lower at Day 28 (4.4 vs. 4.3), Day 84 (4.0 vs. 4.1) and Day 168 (3.8 vs. 3.9). No statistically significant difference between treatment groups was shown at any visit. Additionally, the mean number of days artificial tears were not used was 0.4 days (NOVA22007) and 0.6 days (Vehicle) on Day 28, with no statistically significant difference shown between treatment groups (p=0.596). Mean number of days on Day 84 (0.7 vs. 0.5 [p=0.386]) and Day 168 (0.8 vs. 0.8 [p=0.553]) were also not statistically significantly different between treatment groups.

In the SANSIKA study, the initial analysis of artificial tears predefined in the SAP, was performed at the time of Part 1 database lock and revealed a significant number of missing data. An attempt was made after Part 1 database lock to retrieve missing data, giving the opportunity to provide updated results that are summarised as follows:

Median use of artificial tears is discussed instead of the mean because the distribution of the data was skewed. Median use of artificial tears during the Screening-Baseline period was relatively similar in both treatment groups (9.2 drops/day/eye with NOVA22007 and 10.2 drops/day/eye with vehicle). No major differences were seen in the use of artificial tears between treatment groups during all periods of Part 1. However, the number of missing data was high. Considering all available data, there was a progressive decrease in the use of artificial tears over time in both treatment groups. The number of drops/day/eye was approximately 2 times lower during the Month 3-Month 6 period than the Screening-Baseline period in both treatment groups. Median

use of artificial tears during the Month 3-Month 6 period was 4.4 drops/day/eye with NOVA22007 (n=80) and 5.4 drops/day/eye with vehicle (n=55).

For Part 2 of SANSIKA (open-label), the median use of artificial tears remained relatively stable between Month 3-Month 6 and Month 6-Month 9, and again between Month 6-Month 9 and Month 9-Month 12 in both treatment groups. However, the number of missing data over the Month 6-Month 12 period was high in both groups. Available data showed a steady decrease in the use of artificial tears during the first 6 months in both treatment groups (-3.8 and -2.6 drops/day/eye in the NOVA22007/NOVA22007 group and the vehicle/NOVA22007 group, respectively), thereafter the changes observed during the last 6 months were minor (+0.3 and -0.6 drops/day/eye, respectively).

Schirmer's test

For the SICCANOVE study, in the Full Analysis Set, 142 patients (NOVA22007) and 145 patients (Vehicle) had a Schirmer‟s tear test score ≤5 mm/5 min at Baseline. At Day 168, the number of these patients who had a score ≥10 mm/5 min was comparable between the NOVA22007 (17/142 patients [12.0%]) and Vehicle (22/145 patients [15.2%]) groups. There was no statistically significant difference (p=0.429) between the treatment groups in the number of patients with a score of ≥10 mm/5 min. There was also no statistically significant difference in the number of patients who showed a ≥10 mm/5 min increase at Day 168 (7.7% vs. 4.8% [p=0.308]).

For the Full Analysis Set in the SICCANOVE study, the mean change from Baseline to Day 84 was 1.36 and 1.32 mm/5 min for the NOVA22007 and Vehicle groups, respectively. No statistically significant treatment effect was evident (p=0.885). The mean change from Baseline to Day 168 was 1.95 and 1.76 mm/5 min for the active and Vehicle treatment groups, respectively. There was no statistically significant treatment effect (p=0.665). A post-hoc analysis was performed on subset of patients with severe dry eye (CFS grade 4 at baseline). Mean change in Schirmer's tear test from Baseline to Day 168

was 1.51 and -0.02 mm/5 min for the NOVA22007 and Vehicle groups, respectively. A statistically significant treatment effect in favour of NOVA22007was shown using an ANCOVA model (n=85, p=0.047).

In the SANSIKA study, Mean (±SD) Schirmer test score at Screening was similar in both treatment groups (3.7±2.0 mm/5 min with NOVA22007 and 3.9±2.2 mm/5 min with vehicle). Schirmer test scores, ranging from 2.0 mm/5 min to 9.0 mm/5 min in both treatment groups, were ≥2.0 mm/5 min and <10.0 mm/5 min in all FAS patients in accordance with the inclusion criteria of the study protocol.

There was an increase (i.e. improvement) in the Schirmer test score over time in both treatment groups. At Month 6, the mean change in Schirmer test score from Screening was +2.2 mm/5 min with NOVA22007 and +1.5 mm/5 min with vehicle. The difference between treatment groups was not statistically significant.

For Part 2 (open-label), mean Schirmer test score increased (i.e. improved) between baseline and Month 12 in the NOVA22007/NOVA22007 group (+2.3 mm/5 min) and the vehicle/NOVA22007 group (+1.5 mm/5 min). This improvement was achieved during the first 6 months of the study (+2.4 and +1.4 mm/5 min in the NOVA22007/NOVA22007 group and the vehicle/NOVA22007 group, respectively), as mean Schirmer test score remained stable during the last 6 months (-0.1 and +0.2 mm/5 min, respectively).

Investigator global rating of study treatment

In the SICCANOVE study, for the Full Analysis Set, the Investigator considered the efficacy of treatment as either very satisfactory or satisfactory for 73.8% at Day 28, 63.9% at Day 84, and 62.2% at Day 168 in the NOVA22007 group. In comparison, the percentages of patients in the Vehicle group were slightly lower at each visit (68.5% [Day 28]; 62.5% [Day 84]; 59.7% [Day 168]). No statistically significant difference between treatment groups was shown at any visit.

In the SANSIKA study, patient's improvement was rated by the Investigators as satisfactory or very satisfactory in a slightly higher proportion of patients assigned to NOVA22007 (91 patients, 64.1%) than patients assigned to vehicle (49 patients, 57.0%). The difference between treatment groups was not statistically significant.

For Part 2 of the SANSIKA study (open-label), at Month 12, the proportion of patients showing a very satisfactory or satisfactory improvement was similar in the NOVA22007/NOVA22007 group (71.7%) and the vehicle/NOVA22007 group (69.9%).

In the NOVA22007/NOVA22007 group, the proportion of patients showing very satisfactory or satisfactory improvement did not change between Month 6 and Month 12 (going from 70.3% to 71.7%), whereas it increased in the vehicle/NOVA22007 group (going from 59.5% to 69.9%) during the same period, i.e. the period under NOVA22007 treatment.

Impression cytology

In SICCANOVE, a total of 89 patients (41 patients [NOVA22007]; 48 patients [Vehicle]) provided cytology samples for measurement of inflammatory markers. At Baseline, the mean cell surface HLA-DR expression, converted to arbitrary unit of fluorescein (AUF), was 84345.4 AUF in the NOVA22007 CsA 0.1% group and 46888.2 AUF in the Vehicle group. AUF means of the NOVA22007 group were higher than those found for the Vehicle group due to the presence of very high values in the group. Nevertheless, the two groups presented high HLA-DR values expressed in AUF as well as in percentages, above the expected normal values.

The analysis of median values at Baseline, which limit the impact of these high values on the HLA-DR expressions of the whole group, showed that the HLA-DR expressions were similar in the two groups.

At Day 168, the mean change from Baseline was -50895.7 AUF in the NOVA22007 group and -1191.9 AUF in the Vehicle group.

At Day 168, the mean change from Baseline in the percent of abnormal cells was -4.430% in the NOVA22007 group and -6.189% in the Vehicle group.

The HLA-DR AUF decreased more in the NOVA22007 group than in the Vehicle group, when considering the AUF means as well as the AUF median values. At Day 168, the AUF values of the two groups remained above expected normal values with a lower expression in the NOVA22007 group, especially when considering the median values. It is noteworthy that Patient '11 001' showed an important decrease of HLA-DR values, although still in high values, confirming an important effect of NOVA22007 in reducing the expression of this inflammation marker. HLA-DR percentages were found moderately increased when compared to normal expected values. In this study, the HLA-DR percentages did not show differences between the two groups of treatment and, although decreasing, between Baseline and Day 168.

Note: Percentage of positive cells is an important parameter in flow cytometry but it cannot discriminate a population with a high fluorescence expression than another with a low expression. When studying dry eye patients, the fluorescence levels could vary intensively between patients with the same percentage of positive cells. A fluorescence quantification method is then required (AUF).

This analysis, aimed at comparing the effects of NOVA22007 with Vehicle on the conjunctival expressions of the major histocompatibility complex (MHC) class II antigen, HLA-DR (considered as a hallmark of conjunctival inflammation) showed the efficacy of NOVA22007in reducing HLA-DR levels.

In SANSIKA, baseline median and mean HLA-DR levels were comparable across treatment groups. From baseline to Months 1 and 6, in the NOVA22007 group, there was a decrease in HLA-DR level of expression (AUF) and the percentage of HLA-DR+ cells at both time points whereas in the vehicle group, HLA-DR (AUF) tended to slightly decrease over time while the percentage of HLA-DR+ cells remained relatively stable. Median HLA-DR (AUF) from Baseline to Month 6 is depicted in Figure B8.

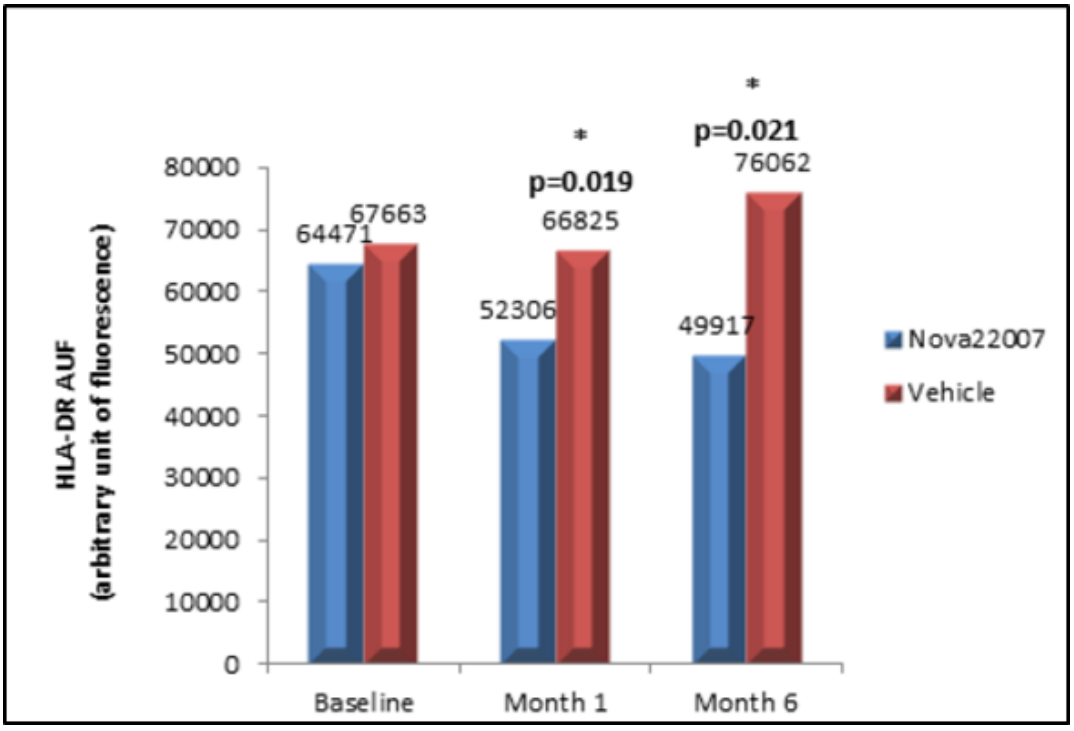


Figure B8 Median HLA DR (AUF) from Baseline to Month 6 (FAS)

When compared to the vehicle group, the NOVA22007 group showed a significant decrease in HLA-DR (AUF) from baseline, both at Month 1 (p=0.019 vs. vehicle) and Month 6 (p=0.021 vs. vehicle). There was no statistically significant difference between treatment groups regarding the decrease in the percentage of HLA-DR+ cells from baseline to Months 1 and 6 (p>0.05, CMH test).

Median HLA-DR (AUF) decreased markedly over 12 months in the NOVA22007/NOVA22007 group (-15945 AUF) and the vehicle/NOVA22007 group (-17147 AUF). During the last 6 months of the study, the vehicle/NOVA22007 group caught up with the NOVA22007/NOVA22007 group, showing a decrease in median HLA-DR (AUF) of 5065.5 AUF (versus a stabilization in the NOVA22007/NOVA22007 group, +314.0 AUF). Despite fluctuations over time, mean percentage of HLA-DR+ cells did not markedly differ between baseline and Month 12 in both treatment groups. In the NOVA22007/NOVA22007 group, a change of -6.75% (±21.31) was observed during the first 6 months and +2.60% (±14.31) during the last 6 months. In the vehicle/NOVA22007 group, a change of -2.62% (±15.18) was observed during

the first 6 months and -1.04% (±16.96) during the last 6 months. Median HLA-DR (AUF) results from baseline to Month 12 are displayed in Figure B9.

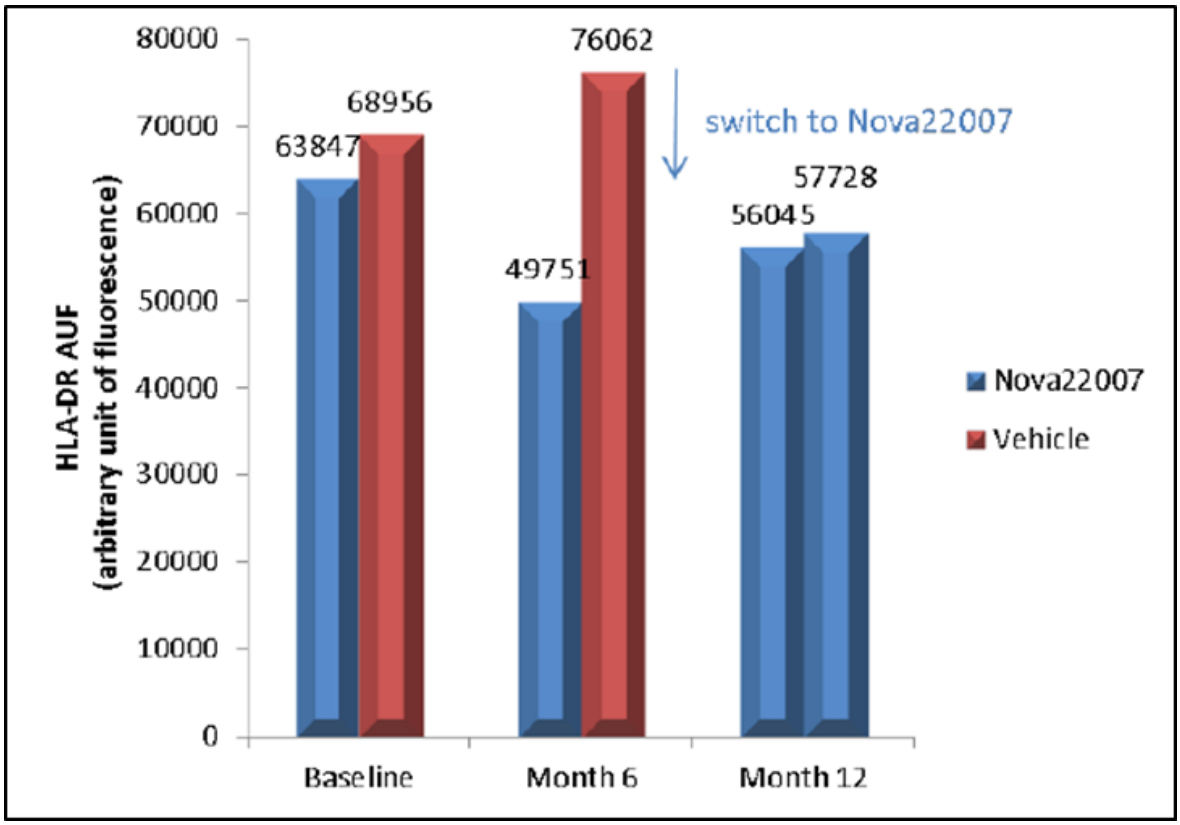


Figure B9 Median HLA-DR (AUF) from baseline to Month 12 – Part 1 and Part 2 (FAS-OPEN)

Tear film osmolarity

In SANSIKA, tear film osmolarity was performed in selected centres. Mean (±SD) tear film osmolarity at baseline was similar in both treatment groups (308.1±20.9 mOsms/L with NOVA22007 and 305.6±15.5 mOsms/L with vehicle). Tear film osmolarity tended to decrease (i.e. improve) between baseline and Month 6 in both treatment groups, with no statistically significant difference between treatment groups (p= 0.485 at 1 month and p= 0.763 at 6 months).

The worst tear film osmolarity between both eyes was analyzed in the FAS patients with a tear film osmolarity at baseline >308 mOsms/L in at least one eye. There was a decrease (i.e. improvement) in the worst tear film osmolarity over time in both treatment groups, however, the NOVA22007 group showed

a statistically significantly greater change from Baseline to Month 6 than the vehicle group (p=0.048).

At Month 6, both the mean and median values of worst tear film osmolarity in the NOVA22007 group were lower than 308 mOsms/L (i.e. the threshold value defining an underlying inflammation), whereas they remained slightly higher than 308 mOsms/L in the vehicle group. At Month 6, the adjusted mean change in worst tear film osmolarity from Baseline was -26.7 mOsms/L with NOVA22007 and -16.7 mOsms/L with vehicle.

During Part 2 of SANSIKA, tear film osmolarity was assessed as an exploratory variable. Mean tear film osmolarity decreased steadily over 12 months in the NOVA22007/NOVA22007 group (-5.3 mOsms/L) and the vehicle/NOVA22007 group (-10.6 mOsms/L). This decrease started during the first 6 months and was pursued during the last 6 months, where a change of -2.9 and -4.16 mOsms/L was observed in the NOVA22007/NOVA22007 group and the vehicle/NOVA22007 group, respectively.

The worst tear film osmolarity between both eyes was analyzed in the FAS-OPEN patients with an elevated tear film osmolarity at baseline (i.e. osmolarity >308 mOsms/L in at least one eye). At baseline, 44 patients had at least one eye with a tear film osmolarity higher than 308 mOsms/L: 28 patients in the NOVA22007/NOVA22007 group and 16 patients in the vehicle/NOVA22007 group. The worst tear film osmolarity decreased steadily over 12 months in the NOVA22007/NOVA22007 group (-27.6 mOsms/L) and the vehicle/NOVA22007 group (-21.3 mOsms/L). In the NOVA22007/NOVA22007, a greater improvement in the worst tear film osmolarity was observed during the first 6 months of the study (-25.2 mOsms/L) than during the subsequent 6 months (-2.7 mOsms/L). In the vehicle/NOVA22007 group, the opposite was observed: a greater improvement was observed during the last 6 months of the study (-12.8 mOsms/L, versus -9.0 mOsms/L during Part 1).

Quality of life

In the SANSIKA study, quality of life was measured using two questionnaires; NEI-VFQ-25 and EQ-5D.

For the NEI-VFQ-25, mean (±SD) composite score at baseline was relatively similar in both treatment groups (71.9±15.7 with NOVA22007 vs. 74.0±13.4 with vehicle). Similar results were found for the 12 individual scale scores (Table B19).

Table B19 NEI-VFQ-25 Composite Score Over Time and Change from Baseline (FAS)

	NOVA22007	**Vehicle**	**ANOVA^**	
	N=154	**N=91**	**Effect**	**p-value**
Baseline	**N=98**	**N=55**		
Mean±SD	71.87±15.74	74.02±13.40	Pooled country	p<0.001
Median	72.92	75.80		
Range (min;max)	(11.9;96.4)	(43.0;96.6)	Baseline score	p=0.164
Month 6	**N=80**	**N=52**		
Mean±SD	76.06±19.23	77.05±16.60		
Median	82.37	82.82		
Range (min;max)	(4.1;99.4)	(33.9;97.0)		
Change from Baseline at Month 6	**N=73**	**N=46**		
Mean±SD	5.18±8.85	4.79±9.94		
Adjusted mean (95% CI)^	4.085 (1.941;6.229)	3.971 (1.326;6.616)		
Median	4.66	5.02	Treatment	p=0.945
Range (min;max)	(-15.7;32.3)	(-21.2;24.7)		

^ Means were adjusted for baseline values using an ANCOVA (analysis of covariance) model with the following fixed factors: “treatment” and “pooled country”, and the baseline data as covariate

Mean (±SD) NEI-VFQ-25 composite score at baseline was relatively similar in both treatment groups (71.9±15.7 with NOVA22007 vs. 74.0±3.4 with vehicle).

Similar results were found for the 12 individual scale scores. There was an increase in the mean NEI-VFQ-25 composite score over time in both treatment groups. At Month 6, the mean change in the NEI-VFQ-25 composite score from Baseline was +4.1 with NOVA22007 and +4.0 with vehicle, when adjusting for baseline scores.

The analysis of the 11 individual scale scores that were vision-specific (all items except “General health”), revealed that at Baseline, 7 vision-specific items scored low (i.e. below 75/100 on average) in the NOVA22007 group and the vehicle group: “General vision” (60.4 and 62.2, respectively), “Ocular pain” (43.1 and 45.6), Difficulty with near-vision activities” (65.9 and 69.2), “Difficulty with distant vision activities” (68.0 and 74.1), “Mental health symptoms due to vision” (55.6 and 62.7), “Role limitations due to vision” (54.9 and 61.5) and “Driving difficulties” (65.7 and 65.5). The item “General health”, which is not vision-specific, also scored low at Baseline in both groups (38.5 and 39.4). All these items improved over 6 months with each treatment and there were no statistically significant differences between treatment groups regarding the change from Baseline of any of these scale scores (or any other scale score), adjusting for baseline scores. However, a trend was found for a greater improvement with NOVA22007 for the ocular pain dimension: +14.4 over 6 months (versus +10.0 in the vehicle group).

For the EQ-5D, mean (±SD) summary index of the questionnaire at baseline was similar in both treatment groups (0.66±0.30 with NOVA22007 and 0.66±0.26 with vehicle). Mean (±SD) EQ-5D VAS score at baseline was relatively similar in both treatment groups (63.9±19.2 with NOVA22007 and 68.2±17.0 with vehicle). There was no change in the summary index or the EQ-5D VAS score between baseline and Month 6 in both treatment groups, see Table B19. No differences between treatments were found.

Table B20 EQ-5D Summary Index and EQ-5D VAS Score Over Time and Change from baseline – Part 1 (FAS)

	NOVA22007 N=154	Vehicle N=91	CMH test^	
			Effect	p-value
EQ-5D – Summary index				
Baseline	N=149	N=87		
Mean±SD	0.66±0.30	0.66±0.26		
Median	0.73	0.73		
Range (min;max)	(-0.4;1.0)	(-0.2;1.0)		
Month 6	N=124	N=78		
Mean±SD	0.68±0.32	0.69±0.27		
Median	0.76	0.74		
Range (min;max)	(-0.5;1.0)	(0.0;1.0)		
Change from Baseline at Month 6	N=121	N=75		
Mean±SD	0.02±0.25	0.02±0.21		
Median	0.00	0.00	Treatment	p=0.808a^
Range (min;max)	(-0.9;0.8)	(-0.8;0.7)		
EQ-5D – VAS score				
Baseline	N=148	N=85		
Mean±SD	63.92±19.18	68.22±17.00		
Median	67.50	70.00		
Range (min;max)	(10.0;100.0)	(30.0;95.0)		
Month 6	N=123	N=77		
Mean±SD	66.48±20.05	67.48±17.22		
Median	70.00	70.00		
Range (min;max)	(0.0;100.0)	(10.0;95.0)		
Change from Baseline at Month 6	N=118	N=74		
Mean±SD	2.38±19.27	-1.55±18.27		

	NOVA22007 N=154	Vehicle N=91	CMH test^	
			Effect	p-value
Median	0.50	0.00	Treatment	p=0.203^
Range (min;max)	(-70.0;76.0)	(-60.0;55.0)		

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

6.6 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.6.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

As the Phase II studies investigated the safety and efficacy of NOVA22007 in different populations to the indication of interest, the safety outcomes have been taken from the two Phase III studies SICCANOVE and SANSIKA which assessed both efficacy and safety. These studies have been previously discussed in sections 6.1 to 6.5.

The key safety objectives of the Phase III clinical development program for NOVA22007 0.1% were to assess the long term safety and tolerability of this topical presentation by evaluating the incidence of adverse events and laboratory abnormalities, and to identify any potential new adverse events.

For the purpose of this submission and the EMA regulatory filing, safety data were pooled rather than describing each individual study separately. Patients analysed in the pooled analysis are patients from the safety populations of each of the individual studies; i.e randomised patients who took at least one dose (1 drop once daily) of NOVA22007 0.1%. Data from these patients were pooled into the “Double Masked Cohort” including all patients from the 6-month double masked phases of SICCANOVE (NVG06C103) and SANSIKA (NVG10E117) studies. This allows a comparison of the extent of safety issues of NOVA22007 versus its vehicle.

This pooled safety data from Phase III studies 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. In addition the double masked period (6 months) was identical in both studies, and the methodology to characterize the safety profile (recording of AEs, measurement of laboratory values, measurement of exposure) was comparable between the studies;

6.6.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Table B21 below summarizes the numbers and percentages of patients with the most frequent TEAEs by system organ class (SOC) and preferred term (>1% in any treatment group) for the double masked cohort.

Table B21 Most frequent TEAEs (>1% in any treatment group) – Double Masked Cohort at 6 months

System organ/ class/adverse events	SICCANOVE and SANSIKA (6 months)					
	Intervention (n (%) of patients) (n = 396)	Comparator (n (%) of patients) (n = 340)	Risk difference	Relative risk	Lower 95% CI	Upper 95% CI
Eye disorders						
Blepharitis	7 (1.8)	3 (0.9)	0.009	2.00	0.52	7.69
Conjunctival hyperaemia	11 (2.8)	4 (1.2)	0.016	2.36	0.76	7.35
Conjunctivitis	2 (0.5)	4 (1.2)	-0.007	0.43	0.08	2.33
Erythema of eyelid	10 (2.5)	7 (2.1)	0.005	1.23	0.47	3.19
Eye irritation	43 (10.9)	10 (2.9)	0.079	3.69	1.88	7.23
Eye pain	18 (4.5)	13 (3.8)	0.007	1.19	0.59	2.39
Eye pruritus	3 (0.8)	5 (1.5)	-0.007	0.52	0.12	2.14
Eyelid oedema	5 (1.3)	2 (0.6)	0.007	2.15	0.42	10.99
Lacrimal disorder	13 (3.3)	10 (2.9)	0.003	1.12	0.50	2.51
Lacrimation increased	10 (2.5)	2 (0.6)	0.019	4.29	0.95	19.46
Meibomianitis	14 (3.5)	12 (3.5)	0.000	1.00	0.47	2.14
Ocular hyperaemia	8 (2.0)	6 (1.8)	0.003	1.14	0.40	3.27
Photophobia	6 (1.5)	5 (1.5)	0.000	1.03	0.32	3.35
Vision blurred	4 (1.0)	3 (0.9)	0.001	1.14	0.26	5.08
Visual acuity reduced	9 (2.3)	12 (3.5)	-0.013	0.64	0.27	1.51
General disorders and administration site conditions						
Instillation site erythema	8 (2.0)	0 (0)	0.020	14.60	0.85	251.96
Instillation site irritation	20 (5.1)	4 (1.2)	0.039	4.29	1.48	12.44
Instillation site lacrimation	5 (1.3)	0 (0)	0.012	9.44	0.52	170.19
Instillation site pain	50 12.6)	9 (2.6)	0.100	4.77	2.38	9.56
Instillation site pruritus	4 (1.0)	1 (0.3)	0.007	3.43	0.39	30.58
Infections and infestations						
Influenza	2 (0.5)	7 (2.1)	-0.016	0.25	0.05	1.17
Nasopharyngitis	5 (1.3)	3 (0.9)	0.004	1.43	0.34	5.94
Urinary tract infection	4 (1.0)	2 (0.6)	0.004	1.72	0.32	9.32
Investigations						
Blood pressure increased	4 (1.0)	3 (0.9)	0.001	1.14	0.26	5.08
Blood pressure systolic increased	3 (0.8)	8 (2.4)	-0.016	0.32	0.09	1.20
Intraocular pressure increased	4 (1.0)	6 (1.8)	-0.008	0.57	0.16	2.01
Musculoskeletal and connective tissue disorders						
Back pain	6 (1.5)	2 (0.6)	0.009	2.58	0.52	12.68

System organ/ class/adverse events	SICCANOVE and SANSIKA (6 months)					
	Intervention (n (%) of patients) (n = 396)	Comparator (n (%) of patients) (n = 340)	Risk difference	Relative risk	Lower 95% CI	Upper 95% CI
Respiratory, thoracic and mediastinal disorders						
Cough	0 (0)	4 (1.2)	-0.012	0.10	0.0052	1.77
Vascular disorders						
Hypertension	4 (1.0)	11 (3.2)	-0.022	0.31	0.10	0.97
Nervous system disorders						
Headache	4 (1.0)	0 (0)	0.010	7.73	0.4175	143.02

The most common TEAEs experienced by patients occurred mainly in the two following system organ classes (SOC): eye disorders and general disorders and administration site conditions. The proportion of TEAEs was higher in the NOVA22007 group.

The most frequent AEs observed with NOVA22007 were instillation site pain (50 patients, 12%), eye irritation (43 patients, 10.9%), instillation site irritation (20 patients, 5.1%) and eye pain (18 patients, 4.5%).

In the vehicle group, the most common AEs reported were eye pain (13 patients, 3.8%), meibomianitis (12 patients, 3.5%) and visual acuity reduced (12 patients, 3.5%).

For SICCANOVE, Overall, 170/492 patients (34.6%) experienced 335 treatment-emergent ocular AEs during the study. The most frequent ocular AEs were eye irritation (51/335 AEs [15.2%]), eye pain (32/335 AEs [9.5%]), instillation site irritation (32/335 AEs [9.5%]), meibomianitis (29/335 AEs [8.6%]), and lacrimal disorder (25/335 AEs [7.4%]). The incidence of ocular AEs was higher in the NOVA22007 group (42.6% vs. 26.8%). The incidence of mild and moderate ocular AEs was comparable between the treatment groups, however the incidence of severe ocular AEs was higher in the NOVA22007 group (34.7% vs. 16.0%). The incidence of definitely related (18.6% vs. 2.8%) and probably related (9.5% vs. 2.4%) ocular AEs was also higher in the NOVA22007 group.

Overall, 128/492 patients (26.0%) experienced 201 treatment-emergent systemic AEs during the study. The incidence of systemic AEs was higher in the Vehicle group (23.1% vs. 28.8%). The majority of systemic AEs were mild

or moderate and were unrelated to the study drug. The incidence of withdrawals due to an ocular AE was slightly higher in the NOVA22007 group (9.9% vs. 7.2%). The incidence of withdrawals due to a systemic AE was slightly higher in the Vehicle group (1.7% vs. 3.2%). There were 22 SAEs of which only one, was ocular (severe epithelial erosion of the cornea) considered by the Investigator to be definitely related to the study drug (NOVA22007). There were no change in BCDVA and IOP during the course of the study.

Vitals signs (blood pressure, pulse rate and respiratory rate) showed no clinically significant change during the study and there was no difference between treatment groups. The majority of patients showed no systemic absorption of CsA. At Day 168, only 4/85 patients (4.7%) had a quantifiable level of blood CsA with values showing that the systemic absorption of CsA was negligible. In the SANSIKA study, during the randomized, double-blind period of the study (i.e. first 6 months of treatment), safety analyses revealed that treatment-related ocular events were reported in a higher proportion of patients treated with NOVA22007 (90 events in 57 patients, 37.0%) than with vehicle (29 events in 18 patients, 20.0%).

The most frequently reported treatment-related ocular TEAE was instillation site pain, which was reported in a higher proportion of patients treated with NOVA22007 (45 patients, 29.2%) than with vehicle (8 patients, 8.9%). Considering all ocular TEAEs except instillation site pain, there were no clear trends for an increased incidence of any ocular TEAE with either treatment, whether the ocular TEAEs were related to treatment or not. Most ocular TEAEs were of mild or moderate severity, regardless of their relationship to treatment.

Ocular TEAEs led to permanent discontinuation of treatment in a higher proportion of patients treated with NOVA22007 (29 events in 18 patients, 11.7%) than with vehicle (8 events in 6 patients, 6.7%). A total of 12 SAEs were reported during the first 6 months of treatment, with only 1 event being related to treatment (a severely reduced visual acuity in 1 patient treated with vehicle).

Safety analyses over 12 months were performed in the 154 patients who received NOVA22007 during Part 1, i.e. the patients who were planned to receive NOVA22007 for 12 months. Throughout the 12-month study, 113 out of 154 patients (73.4%) reported 275 TEAEs. Approximately half these events (128 events) were considered by the Investigator to be treatment-related. They were reported in 70 patients (45.5%).

A total of 86 patients (55.8%) reported 160 ocular TEAEs, 118 of which were considered by the Investigator to be treatment-related. The majority of the ocular TEAEs occurred during the first 6 months of treatment with NOVA22007 (112 events, versus only 48 events during the last 6 months). The most frequently reported treatment-related ocular TEAE was instillation site pain. Over 12 months, approximately one third of the patients who received NOVA22007 (54 patients, 35.1%) experienced instillation site pain.

Most TEAEs were of mild or moderate severity, regardless of their relationship to treatment. Among the 275 events that were reported over 12 months in patients treated with NOVA22007, 25 events were reported as severe in 16 patients (10.4%).

Over 12 months, treatment with NOVA22007 was discontinued due to TEAEs in 31 patients in total (20.1%). There were no ocular SAEs, no AESIs and no deaths over the 12-month study.

The majority of patients had no systemic passage of CsA.

Regarding the other safety analyses (vital signs, BCDVA, IOP and ocular signs as evaluated with the slit lamp), no major differences between NOVA22007 and vehicle were found during the randomized, double-blind period of the study.

6.6.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Overall NOVA22007 is safe and well tolerated. This is shown by the frequencies and nature of AEs and other safety findings, which were broadly

similar for NOVA22007 and its vehicle used as a control. The safety population consisted of adult patients with moderate to severe DED and severe corneal lesions such as keratitis that do not improve despite adequate treatment with tear substitutes that took at least one dose of NOVA22007. The description of the safety profile as reported in section 6.6 is based primarily on the NOVA22007 comparison to vehicle in the 6-month double masked cohort (396 patients). AEs observed with NOVA22007 were consistent with those expected in a DED patient population with associated co-morbidities and receiving a topical formulation of CsA as observed with, RESTASIS 0.05% emulsion, marketed only in USA since 2003 and with AEs reported in the literature and experienced with pharmacy compounded CsA formulations.

The most common ocular AEs that occurred in two of the system organ classes (“Eye disorders” and “General disorders and administration site conditions”), such as eye irritation or pain, or instillation site pain or irritation, were mild to moderate and always transient. Ocular AEs were more severe in intensity and transient in the NOVA22007 group than in the vehicle group. Only one (0.2%) serious ocular AE (epithelial decompensation of the cornea) occurred during the double masked period of the Phase III SICCANOVE supportive study, which resolved within a month. All the events resolved without sequelae, and with the change from the BAK formulation to the CKC formulation, ocular AEs decreased in severity from 27.5% to 6.2%. In addition, most patients showed no or negligible (below LOQ) systemic absorption of CsA as demonstrated in the SICCANOVE and SANSIKA studies.

In summary, the safety and tolerability of NOVA22007 in relation to the population of interest has been addressed through the SANSIKA and SICCANOVE studies. At the moment, there is no registered product for DED in Europe and NOVA22007 1mg/ml eye drop emulsion could effectively replace hospital pharmacy compounded ciclosporin formulations, which are widely used but poorly controlled. NOVA22007 could also replace the uncontrolled use of Restasis in Europe in indications well beyond its FDA-approved label.

6.7 Interpretation of clinical evidence

6.7.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Although the Phase III pivotal (SANSIKA) study failed to meet its primary objective, since statistical significance was not achieved with the composite (CFS-OSDI) endpoint, analysis of this study and the SICCANOVE study revealed a large improvement over time in DED signs and symptoms. A marked improvement of symptoms from baseline was visible in the IKERVIS and vehicle groups. On the other hand in SANSIKA, corneal lesions, i.e. the severity of keratitis, assessed using CFS, also improved markedly from baseline but this improvement was significantly larger in the NOVA22007 arm than in the vehicle arm (p=0.037 at Month 6). The beneficial effect on keratitis was maintained, and even slightly enhanced, under continuous treatment in the open phase of the study, from Month 6 to Month 12. Significantly better effects of NOVA22007 than vehicle on the degree of inflammation and tear osmolarity, i.e. two other key features of DED, were also observed.

There are many possible explanations for the dissociation in the differential benefits of NOVA22007 versus vehicle, such as the well-known lack of correlation between signs and symptoms in DED but also possible beneficial effects of the vehicle itself. In the SANSIKA study these effects of the vehicle were apparently larger than expected (at least, based on predictions from the severe keratitis patients in the SICCANOVE study).

The pre-specified meta-analysis of the SICCANOVE and SANSIKA studies showed that the effects of NOVA22007 on the composite primary endpoint (CFS/OSDI) were significantly better than the effects of the vehicle at Month 6.

The mean difference of 0.35 in CFS observed in SANSIKA at Month 6 represents a ratio of 1.50 in the damaged surface area (CFS is a logarithmic scale). This ratio represents 50% more dots on average in the vehicle group

than in the NOVA22007 group. Clinicians consider this ratio as clinically relevant, at the population level, for the treatment of keratitis. Another way to represent the clinical relevance of the effect on CFS is the odds ratio. In SANSIKA, the odds ratio to obtain a large gain in CFS (at least 1 grade, but also 2 grades, etc.) varied from 1.67 at Month 1 (although not statistically significant) to 1.96 (p=0.026) at Month 6 which is considered clinically relevant.

It is also useful to consider the excess rate of patients reaching at least a given minimal improvement when comparing NOVA22007 and vehicle groups. In SANSIKA the excess rate for gaining more than1 grade was not significant but the excess rates for gaining more than 2 grades was 20.8% (p=0.002) in patients treated for 3 months and for gaining more than 3 grades it was 21.2% (p=0.001) in patients treated for 6 months. These percentages translate into NNTs of 4.8 and 4.7, respectively. A NNT ≤ 6, in this kind of unmet need condition, should be considered as clinically relevant.

Overall, these beneficial effects of NOVA22007 have to be balanced with a very benign safety profile: adverse events were mostly mild to moderate and transient. Even when ocular signs of lower tolerance appeared in some patients, they rarely forced them to stop treatment (withdrawal rate in the active arm, 12.1% vs. 10.3% in the control arm). In addition, measurements of ciclosporinemia showed no evidence of a risk of systemic absorption, e.g. through the nasal mucosa.

6.7.2 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Pivotal efficacy data in the indication sought are provided by pre-specified analyses of the patients in SANSIKA pivotal study, that compared NOVA22007 to its vehicle for the treatment of severe keratitis in adult patients with DED that do not improve despite treatment with tear substitutes. The SANSIKA study did not meet its composite responder primary endpoint in the

FAS but provided evidence of NOVA22007 efficacy on corneal lesions and on symptoms in the target population. Results of secondary variables are also provided. As in SICCANOVE, symptoms markedly improved over time in both groups, active and control.

Key supportive data relevant to the proposed indication are provided by the randomised, vehicle controlled SICCANOVE study. SICCANOVE had two primary objectives – a superiority comparison against vehicle at 6 months as measured by the change from baseline in CFS score (using the modified Oxford scale) and a superiority comparison at 6 months against vehicle as measured by change in global score of ocular discomfort unrelated to study medication. This study met the first primary objective showing a statistically significant superior CFS score change from baseline compared to vehicle at 6 months. The observed significant decrease show that staining was significantly improved over time with NOVA22007. However, the SICCANOVE study did not meet its second primary objective, as NOVA22007 was not superior to its vehicle at Month 6 based on global score of ocular discomfort, a significant improvement in symptoms was noticed in the 2 groups at Month 6 from baseline.

6.7.3 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The main factor which affects the external validity of study results is the use of the Ikervis excipient (vehicle) as comparator. In the absence of an approved and valid active comparator, vehicle was used as recommended by the European Medicines Agency (EMA). In the opinion of the EMA, there was no requirement to compare NOVA22007 with a standard treatment since no such treatment exists. As the NOVA22007 vehicle is not commercially available

and in line with the NOVA22007 licensed indication for use in patients with DED and severe keratitis which has not improved despite treatment with artificial tears it is challenging to provide an informed comparison to treatments in routine clinical practice. A conservative approach is thus justified which makes the assumption that vehicle is equivalent to artificial tears.

In as far as possible the trial was conducted in accordance with expected clinical practice, though the frequency of use of diagnostic tests may be greater than experienced in routine clinical practice. No additional criteria are required to select patients for whom treatment would be suitable beyond a confirmed diagnosis of DED with severe keratitis. The entirety of the evidence presented in this submission used an ophthalmic emulsion containing 0.1% ciclosporin as stated in the SPC.

7 Cost Effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

Primary searches were undertaken on 15th July 2014 in MEDLINE; MEDLINE - In progress (MEIP); Econ-lit and EMBASE using economic filters where applicable. Additionally, a search of the NHS Economic Evaluation Database and the Cochrane Database of Abstracts of Reviews of Effects was performed. Searches were based on the inclusion criteria in Table B22. The full syntax used for all searches are reported in Appendix one.

Table B22 Cost-effectiveness systematic review inclusion criteria

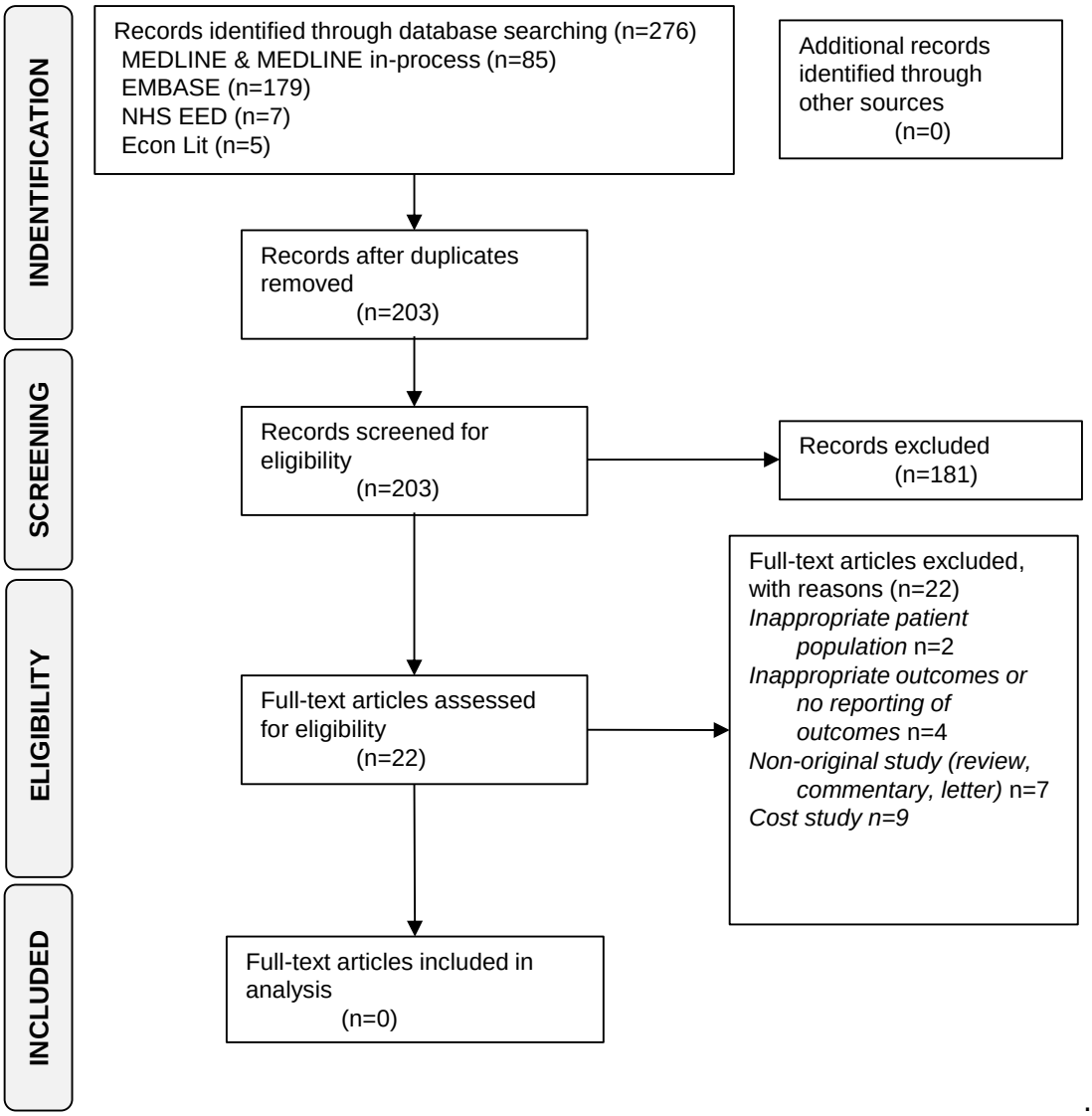
	Inclusion Criteria
Patients	People with severe dry eye disease whose disease has not adequately responded to tear substitutes
Subgroups	None
Interventions	Ikervis
Study type	Cost-effectiveness and cost-utility analyses
Country	UK; US; EU5
Year of publication	2012 onwards

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more

than one study is identified, please present in a table as suggested below.

After de-duplication 203 abstracts were identified, of which 22 underwent full paper review. No cost-effectiveness evaluations that fulfilled the inclusion criteria were identified.



7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Not applicable.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

In line with the scope of the appraisal, adult patients with DED and severe keratitis whose disease had not adequately responded to tear substitutes are included in the economic evaluation. Based on the licensed modelled population used the same cohort of patients as SANSIKA trial population detailed in section 6.3.4

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A graphical summary of the model is presented in Figure B10.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

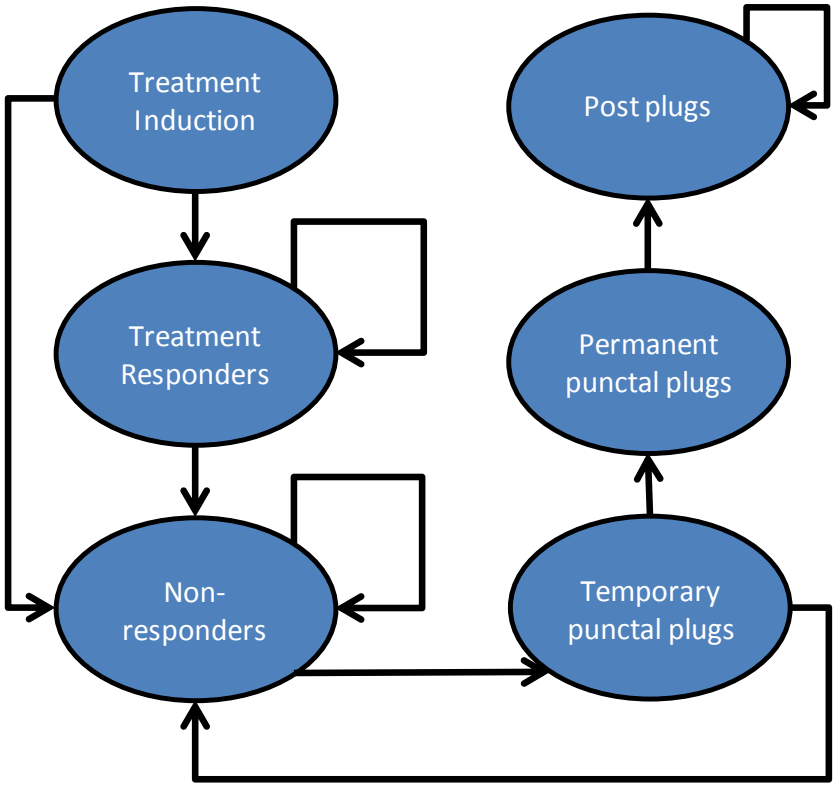


Figure B10 Treatment Schematic (excluding death)

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Conceptual Model

As noted in section 2.4, routine UK practice in patients with severe DED is a combination of artificial tears and ocular lubricant ointments. Treatment options for patients who have not adequately responded to therapy (i.e. those who match the scope of this appraisal) are very limited. As noted in sections 2.4 and 2.5, one potential treatment option is surgery (taken to be either insertion of temporary or permanent punctal occlusion). The use of such procedures in a range of European jurisdictions was reviewed by Clegg in 2006, with the annual implant rate in the UK being less than 1% (22). Hence, while they form part of the clinical pathway for patients with severe DED, from the perspective of UK clinical practice these therapies can be viewed as a last resort option.

This lack of viable active therapy for patients with severe DED who have not adequately responded to tear substitutes resulted in the EMA recommending the use of the Ikervis excipient (henceforth referred to as “Vehicle” for brevity) as the comparator of choice in the Ikervis clinical trial program (see section 2.7 for a detailed discussion around this topic).

Hence, in designing the underlying conceptual model we have chosen to align with routine UK clinical practice rather than the Ikervis clinical trial program. As such, we have made the assumption that vehicle is not routinely available and so the relevant economic and clinical comparison is standard care with and without Ikervis. We were, however, mindful that the clinical efficacy estimates for Ikervis were generated in an environment where vehicle was used and as such have looked to align the economic model, as closely as possible, with the efficacy results from the Ikervis clinical trial program (and in particular the SANSIKA study). In effect, we are viewing the response/ reduction in artificial tear usage in the vehicle arm as regression to the mean.

Model Description

Eligible patients enter the model in the ‘treatment induction’ health state where they receive a six months of therapy with Ikervis plus standard care or standard care alone. The choice of six months is based on the clinical practice and the randomised component of the SANSIKA study. Responders to treatment (defined using a combination of improvement in OSDI and CFS instruments over the six month period) continue on therapy until they are no longer efficacious and active treatment is ceased or, in a small number of patients, temporary punctal plugs are trialled. A small proportion of patients will progress to having the treatment made permanent if they respond well to the temporary plugs, while the remainder return to using artificial tears alone (Section 7.3.1). It is assumed that patients trialling plugs will have no need need for tear substitutes as their dry eye disease is being effectively managed by the punctal plugs. Whilst a small number of patients may trial temporary punctal occlusion again in the future, this is not featured in the model.

The conceptual model was constructed using a state transition (Markov) framework and used a cycle length of three months to best take advantage of the available clinical trial data (in particular information from the SANSIKA study, see section 6.3.2 for a description of this trial).

Since response data is extrapolated over an extended time horizon, mortality is factored into the model. The rate at which mortality is included is assumed to be representative of the general population and independent of the treatment being taken.

7.2.4 Please define what the health states in the model are meant to capture.

The model captures three health states; response, non-response and death, with responders having a higher quality of life than non-responders. 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 was required. Utilities are derived from data extracted from the SANSIKA trial and are used to capture the incremental benefit to patients of responding to treatment. Responders require fewer artificial tears (section 7.5.5) and have an overall higher utility (Table B32).

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As discussed in section 2.1 Severe DED is a chronic inflammatory condition causing discomfort and irritation. This can cause difficulty in reading, driving, watching TV and interfere with day to day work activities such as using a computer, reducing productivity and health related quality of life. The model is designed to pick up improvements from baseline in both sign and symptoms via the composite CFS-OSDI outcome measure and through reductions in usage of concomitant artificial tears.

Disease progression is modelled through change in severity from baseline. Standard care (a combination of artificial tears) provides symptomatic relief and a quality of life, which is assumed to remain consistent over time. Responders to treatment in both arms have a reduction in the signs and symptoms of dry eye disease and a hence higher utility. The increased utility achieved from a positive response is assumed constant for the duration of response. Hence, any treatment that offers incremental clinical benefits in terms of higher response rates will also offer patients an improvement in HRQoL compared to treatments that offer a poorer response profile.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

A summary of the key structural aspects of the Markov model is presented in Table B23.

Table B23 Key features of analysis

Factor	Chosen values	Justification
Time horizon	30 years	Treatment decisions in severe dry eye disease have a potential long term impact on quality of life. A 30 year time horizon is sufficiently long to reflect differences in costs and outcomes between technologies, as per the NICE reference case.
Cycle length	3 months	See section 1.2.3
Half-cycle correction	Yes	Ensures correct modelling of costs and effects.
Were health effects measured in QALYs; if not, what was used?	Yes	Corresponding to the NICE reference case
Discount of 3.5% for utilities and costs	3.5% p.a.	Corresponding to the NICE reference case
Perspective (NHS/PSS)	NHS/PSS	Corresponding to the NICE reference case

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The intervention does not yet have EMA approval and therefore has been implemented in the model as per the wording of its expected marketing authorisation. With the lack of an appropriate and valid active comparator (see sections 2.6, 6.3.2), the efficacy of Ikervis on top of artificial tear substitutes in the treatment of severe DED was assessed against artificial tear substitutes alone (i.e. standard care).

The composition of artificial tears usage was taken from Clegg 2006 (22) and detailed in Table B24. It was reported that for patients with severe dry eye disease in the UK, 57% are prescribed with polyvinyl alcohol (Liquifilm Tears®), 50% with carbomers (Viscotears®) and 50% with paraffin. Due to the severity of disease, preservative free eye drops are the most appropriate treatment to minimize the risk of irritation, as recommended by NICE Clinical Knowledge Summary for Dry Eye Syndrome published in September 2012 (8!scenariorecommendation:3).

Table B24 Artificial Tears in severe DED in the UK

Treatment	Proportion of patients used in	Source
Polyvinyl Alcohol	57%	Clegg 2006
Carbomers	50%	Clegg 2006
Paraffin	50%	Clegg 2006

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

A clinical continuation rule has been factored in the model such that if a patient is classified as a treatment responder at the end of the initial six month trial period they will continue on treatment. At the end of every subsequent three month cycle, patients remain on treatment unless they are no longer responding to therapy or voluntarily cease therapy. This is a fundamental aspect of the model, and patients continue to use Ikervis or AT whilst they receive a benefit from treatment.

Additional costs associated with the continuation rule arise from drug costs for patients responsive to treatment post-trial. This includes both the acquisition cost of Ikervis and the cost of background artificial tears. Health consequences associated with the continuation rule simply reflect the incremental benefit of response that a patient receives whilst on treatment and continuing to experience a symptomatic reduction of dry eye disease.

The response endpoint on which the continuation rule is based refers to the post-hoc analysis of the composite response endpoint from the SANSIKA study, namely a reduction from baseline in CFS of three or more, in conjunction with a reduction from baseline in OSDI of 30% or more at the end of the initial six month period. The composite CFS-OSDI outcome measure accounts for both sign and symptoms of disease and as such represents a robust and plausible measure of responsiveness for which decision on whether patients should continue on treatment can be made.

Due to the simplicity of the continuation rule, it is relatively straightforward to incorporate into routine clinical practice. Patients who meet the eligibility criteria (section 6.3.3) for Ikervis receive six months of treatment and if they respond to treatment, continue to be prescribed Ikervis into the future. No additional monitoring and testing is required outside of usual GP check-ups and hence such a rule can be implemented with minimal cost and bureaucracy to the NHS.

Continuation is centred on responsiveness to Ikervis and is applicable to all patients. Further research and subgroup analysis would be required to determine whether the continuation rule would provide additional benefit to different patient subgroups.

Withdrawal from treatment is factored into the continuation rule. If patients stop responding to treatment or experience adverse events they cease treatment with Ikervis and revert to standard of care using artificial tears at the level observed at baseline in SANSIKA, they may also continue to trial temporary punctal occlusion.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Treatment response rates (first 6 months)

Trial data for the vehicle was used to model the response in the comparator arm of the model, i.e. sole usage of artificial tears. The primary endpoint in the SANSIKA study reported the proportion of patients who were responsive to both the vehicle and Ikervis after both 3 and 6 months.

For the purposes of the economic analysis we have used the observed data for the response endpoint. In the model, patients who discontinued treatment before 6 months are considered to be non-responders, however, for those who completed the initial 6 months of the trial and either had no data available or data missing (those for whom imputation was used in the primary analysis) the study imputation rules state that the LOCF is used to populate the latter estimates or if not available the patient is labelled a non-responder. For this reason the observed data was used. This analysis utilised complete data from 131 of the 154 patients on Ikervis and 82 of the 91 patients on vehicle in the FAS. A patient was classified as a responder if they achieved an improvement in:

- CFS of at least 2 and OSDI of at least 30%.

The post-hoc response criteria used in the model features the same two measures as the primary endpoint reported in the clinical trial, however the criteria for response in the clinical trial is more stringent, requiring an improvement in:

- CFS of at least 3 and OSDI of at least 30%

Using the post-hoc definition of response, 16.2% of patients on Ikervis had responded to treatment at 3 months compared with 7.69% on the vehicle, increasing to 18.8% and 7.7% respectively by 6 months.

In comparison, using the less strict response criteria in the SANSIKA trial, 22.5% of patients had responded to Ikervis at 3 months compared with 13.5% on the vehicle, increasing to 32.8% and 24% respectively by 6 months (Table B25)

Table B25 Composite CFS-OSDI responders after 3 and 6 months

	SANSIKA Trial*	Post-Hoc analysis of SANSIKA trial+
Ikervis + Artificial tears (3 months)	22.5%	16.2%
Ikervis + Artificial tears (6 months)	32.8%	18.8%
Artificial tears (3 months)	13.5%	7.7%
Artificial tears (6 months)	24%	7.7%

*CFS improvement ≥ 2, OSDI change ≥ -30%. + CFS improvement ≥ 3, OSDI change ≥ -30%

Treatment continuation rates (post 6 months)

To estimate the likelihood of continuing on Ikervis after the initial six month period, observed data from second phase of SANSIKA was required to parameterise the model. The reported withdrawal rate between six and 12 months was used as a proxy to calculate the cycle specific probability of ceasing Ikervis therapy in each model cycle after the end of the trial.

Between six and 12 months a total of 10.9% patients initially randomised to Ikervis who continued on Ikervis post six months withdrew from the study. 7.8% withdrew because of treatment emergent adverse events effects and the remaining 3.1% because of other reasons.

79 of the individuals initially randomised to vehicle entered the second phase of the study and received Ikervis. These patients were not included in the cycle calculation probabilities calculations because they were using Ikervis for less than six months. This patient subset was also non-randomised, meaning that we cannot be sure the two groups are comparable in terms of important baseline characteristics, which could act as effect modifiers. Hence any analysis on this patient subset is likely not a good predictor for long term response.

Since the SANSIKA trial reported treatment failure probabilities over six months, and the model uses quarterly cycles, a conversion was required to derive a cyclical treatment failure probability. This is a simple transformation

converting to an instantaneous rate and back to a three monthly probability using the standard rate probability calculation formula (80). This results in a probability of stopping treatment of 5.6% in each 3 monthly cycle.

Due to the nature of the SANSIKA trial design, six to 12 month failure probability data was not available for the vehicle to derive the probability of discontinuation for vehicle after the trial period has finished. Therefore, SANSIKA trial data up to six months was used as a proxy to calculate this probability. During this timeframe, 11 out of 90 patients (12.2%) withdrew from the study. Nine patients (10%) withdrew because of treatment emergent adverse effects and two (2.2%) because of other reasons. This results in a probability of stopping treatment of 6.3% in each 3 monthly cycle.

Use of more invasive procedures in non-responsive patients

According to ophthalmologists (22) surgical procedures are reserved for a very small number of patients. The most common procedure performed is punctal occlusion (either temporary or permanent) with temporary plugs trialled before permanent plugs are inserted. More invasive surgical procedures such as gold lid weights and tarsorrhaphy (eyelid sealing) are used as a last resort in a very minor number of patients.

Clegg 2006 (22) reported punctal plug usage of less than 0.01 per person with dry eye disease per year. Since the modelled patient group is at the severe end of the spectrum, the annual rate for the target population was assumed to be equal to 0.01 surgical procedures per patient, of which punctal occlusion accounted for 94%. The annual rate of 0.01 was consequently converted into a three month probability (using the method described above) to derive the probability of receiving punctal plugs in a given cycle.

If a patient reacts well to temporary punctal occlusion, permanent punctal plugs are inserted in the next model cycle. A systematic review by the Cochrane collaboration found limited evidence on the efficacy of punctal plugs, and hence 10% of those who have temporary punctal plugs are assumed to have their treatment made permanent (81). For those who are not responsive, usage of artificial tears resumes. Permanent punctal occlusion is

assumed to be 100% efficacious, reducing artificial tear usage to zero and giving patients the utility of treatment responders.

Due to the usage in the UK (22) more invasive surgical procedures such as tarsorrhaphy, gold lids weights and Botulinum toxin are not included in the economic model.

Adverse events

Common adverse events associated with Ikervis are stinging and installation site pain (see section 6.5.3). These events are typically of low severity and only last for a few seconds. Patients discontinuing treatment due to adverse effects is factored into the model through a reduction in the treatment continuation rates. Therefore, a reduction from baseline utility associated with adverse effects has not been explicitly modelled.

Inclusion of all-cause mortality into the model

Since dry-eye disease has no effect on mortality, patients were assumed to have the same mortality rate as the general population (39) at age 61 – the mean age of patients in the SANSIKA trial.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Derivations of the relevant probabilities are described in section 7.3.1.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is no data to suggest that this assumption would be appropriate for individuals who have severe dry eye disease.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Response to treatment using the primary endpoint in SANSIKA was linked directly to an improvement in health related quality of life based on analysis of the SANSIKA clinical trial data. No other intermediate outcome measures were used.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A key objective of the economic analysis was to utilise estimates from the available literature to inform parameter values in the model. Whilst clinical experts were consulted it was only to confirm the relevance and validity of the estimates and their application in the model.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B26 Summary of variables applied in the economic model

Variable	Value	Standard Error	Distrbution	Reference to section in submission
Ikervis 3 month response rate	0.162	0.016	Beta	Section 7.3.1
Ikervis 6 month response rate	0.188	0.019	Beta	Section 7.3.1
Vehicle 3 month response rate	0.077	0.008	Beta	Section 7.3.1
Vehicle 6 month response rate	0.077	0.008	Beta	Section 7.3.1
Non responder to temporary punctal occlusion transition probability	0.024	0.0002	Beta	Section 7.3.1
Temporary to permanent punctual occlusion transition probability	0.1	0.01	Beta	Section 7.3.1
Ikervis cycle failure probability	0.056	0.006	Beta	Section 7.3.1
Vehicle cycle failure probability	0.063	0.006	Beta	Section 7.3.1
Temporary punctual occlusion cost	£628.95	£62.89	Gamma	Section 7.5.1
Permanent punctual occlusion cost	£628.95	£62.89	Gamma	Section 7.5.1
Number of treated eyes	2	0.1	Beta	Section 7.5.5
Polyvinyl alcohol usage	0.57	0.057	Beta	Section 7.2.7
Carbomers usage	0.5	0.05	Beta	Section 7.2.7
Paraffin usage	0.5	0.05	Beta	Section 7.2.7
No response utility	0.66	0.002	Beta	Section 6.5
Change from baseline utility	0.08	0.03	Beta	Section 6.5

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Both costs and outcomes were extrapolated beyond the SANSIKA trial time horizon of 12 months. This was based on the assumption that all non-mortality related transition probabilities for responders and non-responders were constant over time.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

A list of all assumptions and justifications used in the model is presented in Table B27

Table B27 List of assumptions and justifications

Assumption	Comment
Dry eye disease and its treatments have no additional mortality risk compared with the general population at the same age.	See section 2.3.
Treatment related adverse events do not have a significant effect on quality of life, treatment costs are low and incidence rates in routine practice also low. Hence were not formally modeled but are implicit in the treatment specific discontinuation rates.	See section 7.4.7
Transitional probabilities are constant over time.	This assumption was necessary given the lack of detailed long term data. Information from the literature and ikervis studies also provided no evidence to contradict this assumption
Quality of life remains constant over time conditional on response status.	Utilities are derived from whether patients meet pre-specified response criteria. These are based on CFS and OSDI scores and are time-independent.
Patients have one drop of Ikervis per eye per day.	Reflects the SANSIKA trial design and its expected license.
For patients who require background therapy, a combination of one or more of polyvinyl alcohol, carbomers and paraffin is used.	This is reflective of clinical practice for patients with severe dry eye disease in the UK.
Permanent punctal occlusion has 100% efficacy.	Patients are modelled to only receive permanent plugs if they were responsive to temporary plugs. This likely overestimates the benefit of permanent punctal occlusion but is assumed for simplicity due to the very small number of patients expected to receive this treatment.
Transition probabilities are time independent.	There is no evidence to suggest that transition probabilities in relation to the model should vary as a patient ages.
Patients responsive to punctal occlusion have the same utility gain as those responsive to Ikervis/vehicle.	See section 7.4.9.
Administration, monitoring and testing costs associated with treatment are all zero.	All therapies are self-administered so these costs are not incurred.
Patients affected by dry eye disease are affected in both eyes and hence require treatment in both eyes.	SANSIKA CSR noted that almost all patients had a diagnosis of DED in both eyes (239/245, 97.6%), Clinical input also elicited to corroborate this assumption

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Both costs and outcomes were extrapolated beyond the SANSIKA trial time horizon of 12 months up to a period of 30 years to reflect a lifetime horizon. This was based on the assumption that all non-mortality related transition probabilities for responders and non-responders were constant over time.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Typically, severe dry eye disease substantially impacts the patients HRQoL. The associated utility in the SANSIKA trial was 0.66, similar to that experienced in haemodialysis. (82) Schiffman 2003 (26) used a time trade off approach and also found a significant decrease in quality of life, with a baseline utility for patients with severe DED of 0.72 (section 7.4.6).

Severe dry eye disease is also a chronic condition. The use of active therapy aims to manage symptoms and relieve discomfort, but in the absence of response to therapy, the relative impact of severe DED is assumed to be constant.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

HRQoL data was collected from SANSIKA using the EQ-5D instrument. This measure is a standardized instrument as a measure of health outcome and its use is in line with the expectations of NICE and the requirements of the reference case.

HRQoL in DED can also be measured using disease specific instruments such as the NEI-VFQ, VAS and OSDI, which were also collected in SANSIKA. However the use of these measures is not in line with the NICE reference case and as such their use is less relevant for model parameterization. Neither ORA nor SICCANOVE reported EQ-5D as an outcome measure and hence SANSIKA was used as the primary date source for HRQoL.

Patient utilities were measured at the end of the 6 month SANSIKA trial and subdivided between responders and non-responders to gain the incremental benefit of response. Any response related HRQL benefits were assumed to remain constant for the entire time a patient is responsive to treatment (see section 7.4.2). Changes in utility after 6 months for responders and non-responders are summarized in Table B33.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Data used in the model was directly elicited using the EQ-5D instrument and so no mapping was required.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic search was undertaken in MEDLINE, Medline in process and EMBASE within the OVID platform. Searches were based on the inclusion criteria in Table B28 using the search syntax presented in section **Error! Reference source not found.**

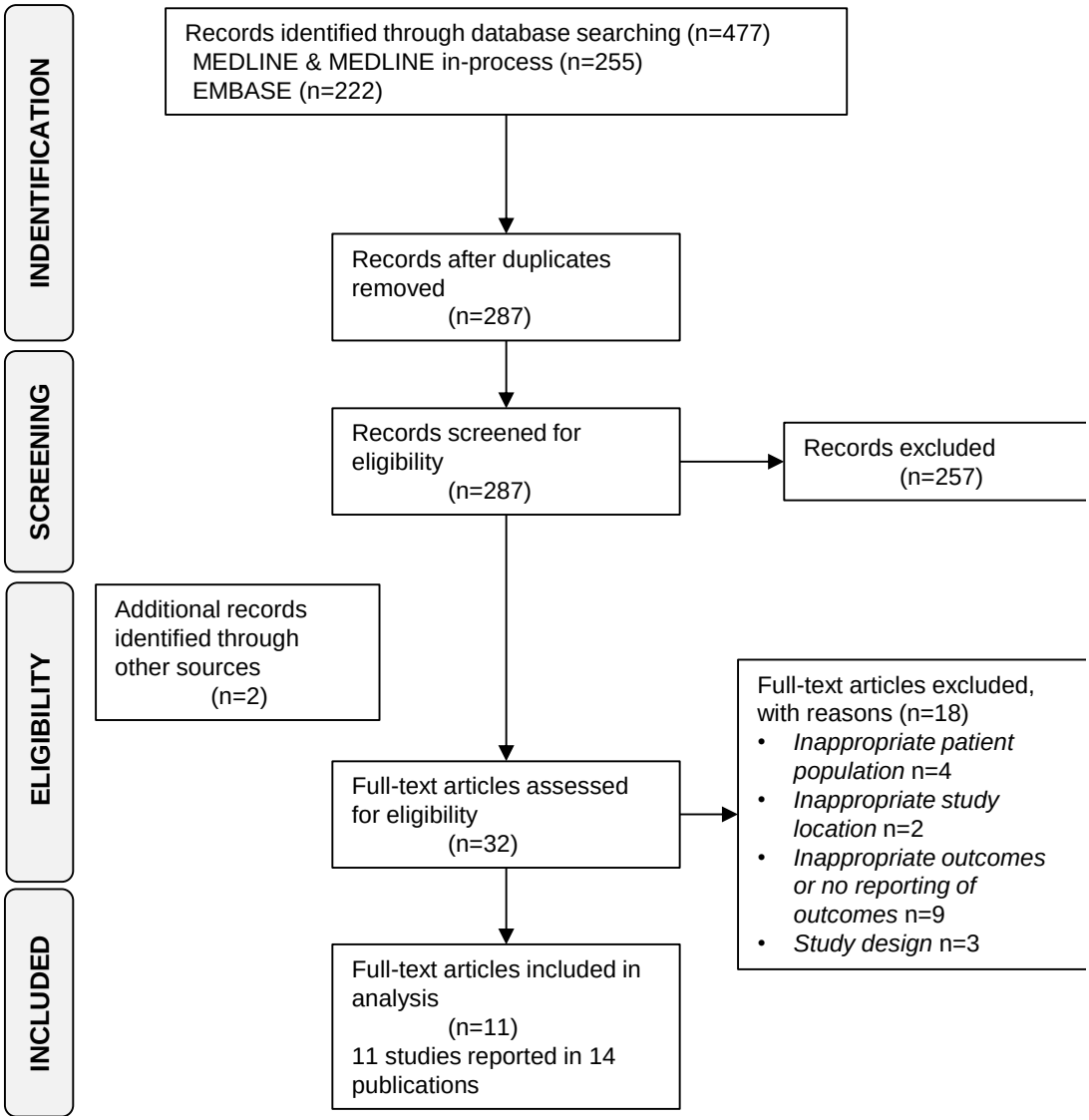


Table B28 Systematic review inclusion criteria

	Inclusion Criteria
Patients	People with severe dry eye disease whose disease has not adequately responded to tear substitutes
Subgroups	None
Interventions	Any
Study type	HRQL, cost-effectiveness and cost-utility analyses
HRQL Instruments	•Reported utilities or scores derived using preference- based measures of health (SF-36, HUI II/III, EQ-5D, HADS, NEI-VFQ-25, OSDI, VAS)
Country	UK; any US or EU5 countries studies using UK valuation weights
Year of publication	From database inception
Health states included	All

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.

- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Of the 11 included studies, four were set in the USA (McDonald (2009), Nichols (2002), Schiffman (2003), Sheppard (2014)), one in Canada (Hutnik (1998)), and one multicentre-study (Rajagopalan (2005)) in both Canada and the USA (Table B29).(26, 78, 83-85) Of the remaining five studies, all were in Europe: two in France (Chiambaretta (2004), Denoyer (2012)), one in Austria (Sator (1998)), one in Italy (Rolando (2007)), and one in the UK (McDonald (2002)).(86-90)

Six of the eleven studies were randomised trials (Chiambaretta (2004), Hutnik (1998), McDonald (2002), Rolando (2007), Sator (1998), Sheppard (2014)). Of the remaining five, Denoyer (2012) was a case-controlled study, while McDonald (2009) studied the acceptability of a single treatment. Nichols (2002) was a repeatability study for the NEI-VFQ-25. The remaining studies, Schiffman (2003) and Rajagopalan (2005), were questionnaires.

Six studies used a visual analogue scale (VAS) to measure DED burden. Three (Denoyer (2012), McDonald (2009), and Sheppard (2014)) reported OSDI values; one of these, Sheppard (2014), was also one of the six studies to report VAS scores. Rajagopalan (2005) reported both EQ-5D and SF-36 results, and Nichols (2002) reported NEI-VFQ-25. Schiffman (2003) used the time trade-off (TTO) method to elicit utilities for DED conditions directly.

Table B29 Humanistic burden: trial characteristics

Study ID	Study design	Time period		Country	Population	Instrument	Elicitation method	Population from which weightings were elicited
		Start year	End year					
Chiambaretta 2004	Multi-centre, randomized, investigator-masked trial comparing carbomer gels C974P (0.25%) and C940 (0.20%)	1993	1994	France	Patients with DED	VAS	Direct	NA
Denoyer 2012	Prospective, case-controlled. OSDI questionnaire administered before clinical examination.	-	-	France	40 DED patients matched (age and gender) with 40 controls.	OSDI	Direct (interviewer-administered)	NA
Hutnik1998	Randomized, prospective, single-centre comparison of argon laser and electrocautery punctal manipulation. Patients randomized by EYE not by person.	1996 (June)	1997 (April)	Canada	Patients with moderate to severe symptoms/signs of DED, recruited from form letter sent to clinicians.	VAS	Direct	NA
McDonald 2002	Randomized, multicentre, crossover study of HA vs 1.4% (w/v) solution of PV	-	-	UK	UK patients with severe DED (see criteria)	VAS	Direct	NA
McDonald 2009, McDonald 2010, Koffler 2010	Multi-centre, two-visit, open-label study to determine the acceptability of hydroxypropyl cellulose ophthalmic inserts	-	-	USA	Patients with a history of moderate to severe dry eye; 'either a diagnosis of DED in both eyes with a history of intermittent to regular artificial tear use, or a desire to use artificial tears within the past week prior to study initiation'	OSDI	Direct	NA
Nichols2002	Prospective dry eye diagnosis repeatability study to measure the performance and test-retest repeatability of the NEI-VFQ-25	-	-	USA	Patients with DED (previous diagnosis according to ICD-9 at Ohio State University College of Optometry)	NEI-VFQ-25	Direct	NA
Rajagopalan 2005, Mertzanis 2005	Series of questionnaires twice over a 2 week period, clinical testing for dry eye	-	-	Canada, USA	Patients recruited from clinicians' records at six sites. At two sites, recruited if had SS using ICD-9-CM or San Diego criteria. At the other four, recruited if had non-SS KCS diagnosis using ICD-9-CM. Controls from lists of patients without diagnostic codes for dry eye.	EQ-5D	Direct	Unclear
						SF-36	Direct	NA

Rolando2007	Open-label, randomised, comparative single-centre clinical study comparing TSP to hyaluronic acid (Hyastil)	-	-	Italy	Patients with dry eye	VAS	Direct	NA
Sator1998	Randomized prospective trial comparing 17beta-oestradiol eye drops to a tear substitute ('Protagent')	-	-	Austria	Postmenopausal women suffering from KCS and necessitating a hormone replacement therapy for general climacteric symptoms.	VAS	Direct	NA
Schiffman 2003	Questionnaires to measure health utilities in addition to ophthalmic evaluation. Test-retest reliability sample	2000 (Aug)	2001 (Mar)	USA	Patients with dry eye (previous diagnosis according to ICD-9 at Henry Ford Health System in the last 6 months, and symptoms for at least 3 months)	Utilities (TTO)	Direct (computerized interview)	Study population
Sheppard 2014	Randomized phase 3 trial comparing lifitegrast ophthalmic solution 5.0% (LIF) with placebo; double-blinded; randomization stratified by previous medication and corneal staining.	2011 (Sept)	2012 (April)	USA	Adult subjects with established history of bilateral dry eye disease	VAS	Direct	NA
						OSDI	Direct	NA

VAS: visual analogue scale. NA: not available. OSDI: ocular surface disease index. HA: sodium hyaluronate. PV: polyvinyl alcohol. NEI-VFQ: National Eye Institute visual function questionnaire, SS: Sjögren's syndrome. KCS: keratoconjunctivitis sicca. TSP: tamarind seed polysaccharide. TTO: time trade-off. LIF: lifitegrast ophthalmic solution 5.0%.

The eleven included studies did not report outcomes for specific age groups. Among those suffering from DED, the average age ranged from 51.9 (SD not reported) in the Sjögren's syndrome arm of Denoyer (2012), to 65 years (SD 7) in the electrocautery punctal manipulation arm of Hutnik (1998) (Table B30). The average age of the control arm of Rajagopalan (2005) was 39.23 (SD 11.76); this group was statistically significantly lower in age compared with the other treatment arms.

Only one of the studies, Sator (1998), reported results by gender; this study was only in women with KCS. In the remaining studies, the percentage of participants who were female ranged from 54.5% in the TSP 0.5% arm of Rolando (2007), to 100% in the argon laser ablation arm of Hutnik (1998) and in the polyvinyl alcohol to sodium hyaluronate crossover arm of McDonald (2002). Patients in these arms were all quite small, with 11, 20 and 15 participants, respectively.

The two largest studies were McDonald (2009) (n=520) and Sheppard (2014) (n>290 in each arm). The percentage female was 64.8% in McDonald (2009), 73.6% in the placebo arm of Sheppard (2014) and 78.2% in the lifitegrast arm.

The diagnostic criteria for DED varied widely among the studies. Nichols (2002), Sator (1998) and Schiffman (2003) required a previous diagnosis and in Rajagopalan (2005) patients had a confirmed diagnosis at recruitment. In McDonald (2009) the DED diagnosis was at the discretion of the investigator. Sheppard (2014), Chiambaretta (2004), Denoyer (2012), Hutnik (1998), McDonald (2002), and Rolando (2007) required a combination of signs, symptoms and tests.

Schiffman (2003) and Nichols (2002) also required a combination of signs and symptoms in order to classify severe DED. Hutnik (1998) and Rolando (2007) used results of the VAS scores to help diagnose DED.

Table B30 Humanistic burden: baseline characteristics and DED diagnosis criteria

		Subgroup definition					Age			
Study ID	**Instrument**	**Age**	**Gender**	**Severity**	**Treatment**	**N**	**Mean**	**SD**	**% female**	**DED classification method**
Chiambaretta 2004	VAS	All	All	All	C974p (Siccafluid)	87	61.8	13.4	85.1	Combination of 'evocative bilateral symptoms' and 2 of the 3 following: Schirmer I <6 mm in 5 min, TBUT <10 s, rose Bengal ≥3.5 (Van Bjisterveld).
		All	All	All	C940 (Lacrigel)	81	59.4	13.4	81.7	
Denoyer2012	OSDI	All	All	DED	All	40	53.4	16.2	80	2007 International Dry Eye Workshop criteria: ocular symptoms, Schirmer I 5 mm/5 min, TBUT <10 s, corneal and conjunctival staining.
		All	All	No DED	All	40	52.4	16.4	80	
		All	All	DED: SS only	All	-	51.9	-	87.7	
		All	All	DED: non-SS only	All	-	56.1	-	76.3	
Hutnik1998	VAS	All	All	All	ALA	20	53	11	100	VAS score (sum over six signs/symptoms) ≥15 for moderate to severe dry eye symptoms. Schirmer I <5 mm for severe aqueous tear disease
		All	All	All	EPM	18	65	7	78	
		All	All	All	Tear-gel	26	62	10	77	
McDonald2002	VAS	All	All	All	Crossover, HA to PV	17	56.4	12.8	88.2	Tear function index (TFI) ≤50, associated with primary or secondary SS, meeting four of the six criteria of the European Classification of SS
		All	All	All	Crossover, PV to HA	15	61.6	15.5	100	
McDonald2009	OSDI	All	All	All	All	520	-	-	64.8	General dry eye evaluation at discretion of investigator
Nichols2002	NEI-VFQ-25	All	All	All	All	75	-	-	70.7	Previous diagnosis. European criteria for KCS to classify severity
		All	All	Severe	All	16	-	-	-	According to European criteria for KCS (Vitali1996): [[van Bjisterveld fluorescein staining score ≥4], or [Schirmer I score ≤5 mm/5 min]] and [symptoms]
		All	All	Milder	All	59	-	-	-	Did not meet European criteria for KCS
Rajagopalan2005	EQ-5D,	All	All	Control	All	48	39.23	11.76	73	Patient diagnosis at study recruitment

	SF-36	All	All	Non-SS KCS	All	130	55.18	15.26	79	
		All	All	SS	All	32	58.25	11.78	91	
Rolando2007	VAS	All	All	All	TSP 0.5%	11	59.01	13.83	54.5	TBUT <10 s, at least two dry eye symptoms >6 cm on VAS, Schirmer I test ≤ 5 mm/5 min, positive testing =2 in at least one area of ocular surface
		All	All	All	TSP 1.0%	10	62.33	13.06	60.0	
		All	All	All	HA 0.2%	9	59.45	10.60	88.8	
Sator1998	VAS	All	Women	All	17 beta-oestradiol	42	52	4.2	100	European KCS criteria
		All	Women	All	Protagent	42	54	5.3	100	
Schiffman2003	Utilities	All	All	All	All	57	52.7	13.9	81	Previous diagnosis, symptoms for at least 3 months (scoring ≥8 on OSDI). Severity by physician assessment and by composite score: (Schiffman2000, adheres to US NEI Workshop recommendations) combining Schirmer I and ocular surface staining with patient perception of ocular symptoms
		All	All	Mild	All	-†	-	-	-	
		All	All	Moderate	All	-†	-	-	-	
		All	All	Severe	All	-†	-	-	-	
Sheppard2014	VAS, OSDI	All	All	All	Placebo	295	61.1	11.8	73.6	Initial screening: history of DED, conjunctival redness, fluorescein staining score >2.0, Schirmer ≥1 and ≤10 mm/5 min, best-corrected visual acuity <0.7 logarithm of the minimum angle of resolution in both eyes. Also dynamic response to Controlled Adverse Environment test needed at two visits
		All	All	All	LIF	293	60.2	12.2	78.2	

Rajagopalan (2005) was the only study to report EQ-5D data. Quality of life values are reported in Table B31.

Table B31 Rajagopalan (2005) EQ-5D values

			EQ-5D QoL score		Additional VAS score for overall QoL	
Study ID	**Time point**	**Subgroup**	**Mean**	**SD**	**Mean**	**SD**
Rajagopalan2005	Baseline	Control	0.87	0.03	88.93	2.06
		Non-SS KCS	0.82	0.02	82.45	1.19
		SS	0.74	0.03	66.94	2.43

SS: Sjögren's syndrome, KCS: keratoconjunctivitis sicca, QoL: quality of life, VAS: visual analogue scale.

Schiffman (2003) derived a set of utilities for a range of DED severity levels, using the time trade-off method (Table B32). The scale for these utilities is from 0 to 1 where 0 represents death and 1 is perfect health. The authors adjusted for comorbidities in these calculations by including an addition of the effects of the comorbidities. A utility of 0.72 (SD 0.23) was elicited for severe DED (not requiring tarsorrhaphy), which Schiffman (2003) compares with a (comorbidity-adjusted) utility of 0.71 for class III/IV angina.

Patients reported their own current DED to have a utility score of 0.81 (0.19). The proportion of this overall group that had severe DED is unclear: Schiffman (2003) reports a total of 57 subjects, with an interview failure (misordering rate) of 29% giving n=40 non-failures, consistent with their reporting of 10, 16 and 14 patients with severe, moderate, and mild DED, respectively, as classified by physicians. However, in the tables in the Schiffman (2003) publication report n=43, so these subgroup populations may not have been reported correctly.

The utility decrements solely due to these specific ocular conditions were also calculated and presented; the scale is again 0 to 1, but for these decrements 0 means no utility is lost and 1 means all utility (equivalent to that of perfect health) is lost. The utility decrement for severe DED was 0.16 (0.14), and for severe DED requiring surgery was 0.26 (0.20).

Table B32 Utilities elicited by time trade-off (TTO)

Study ID	Subgroup	Utility	Health state evaluated	Score	
				Mean	SD
Schiffman 2003	All	Utility assessment of ocular conditions and comorbidities	Comorbidity in absence of dry eye	0.88	0.14
			Monocular painful blindness	0.64	0.29
			Binocular painful blindness	0.35	0.31
			Asymptomatic dry eye	0.78	0.23
			Mild dry eye	0.81	0.18
			Moderate dry eye	0.78	0.19
			Severe dry eye	0.72	0.23
			Severe dry eye requiring surgery	0.62	0.26
			Current dry eye	0.81	0.19
		Lost utility caused solely by ocular condition	Monocular painful blindness	0.24	0.22
			Binocular painful blindness	0.52	0.29
			Asymptomatic dry eye	0.10	0.16
			Mild dry eye	0.07	0.07
			Moderate dry eye	0.10	0.10
			Severe dry eye	0.16	0.14
			Severe dry eye requiring surgery	0.26	0.20
			Current dry eye	0.07	0.07

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

There are no studies in the literature, which capture and report EQ-5D utilities in a similar population to the SANSIKA study. However, baseline utility values for severe DED in the SANSIKA study, 0.66, are broadly comparable to those reported in the TTO study of DED patients by Schiffman et al., 0.62 - 0.72. (26)

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

TRAEs are not in the model as they are mostly mild and transient and as such do not require treatment. The impact on HRQoL is also negligible. Severe TRAEs that ultimately lead to discontinuation are implicitly modeled (see section 7.3.1).

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Utility values were estimated from the EQ-5D data collected at baseline and 6 months in the SANSISKA study. The change from baseline in utility was estimated for both responders and non-responders according to the CFS-OSDI criteria defined as the primary endpoint in SANSIKA. The results of the analysis for all patients are shown in the results split by treatment in Table B33. These values are taken from EQ-5D patient level data measuring HRQoL, as recommended in the NICE scope. The utility benefit of just over 0.07 for response is similar to published incremental response utilities in Schiffman 2003 (26). For simplicity, responders to punctal plugs are assumed to gain the same incremental benefit as responders to active treatment.

Table B33: Change in EQ-5D from baseline to 6 months by CFS-OSDI response (all patients

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

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Values were not assessed by clinical experts for applicability.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

See section 7.4.1 and 7.4.2

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Adverse events were not included in the analysis. See section 7.4.8 for more details.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

See section 7.4.9. Baseline quality of life is assumed to be equivalent to that of a non-responder to treatment.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The relative impact of severe DED on HRQL, compared to the general UK population, is assumed to be constant over time conditional on whether the patient is classified as a responder or a non-responder. See section 7.4.2

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

As noted earlier, patients with severe DED are managed with artificial tears. As such, there is no relevant PbR, DRG or HRG coding for routine management of severe DED.

For simplicity we have used the National Health Service HRG tariffs BZ10C ("Minor Orbits or Lacrimal Procedures, 19 years and over, with CC Score 2+") and BZ10D ("Minor Orbits or Lacrimal Procedures, 19 years and over, with CC Score 0-1") as indicative of the average cost to the UK NHS of punctal occlusion surgery arising from severe DED. We have used tariff values from the 2013 version of the NHS Schedule of Reference Costs (NHS SRC) (91) and assumed that all such procedures will be done as day cases on an elective basis. A summary of the HRG tariff values used in the model for other surgery are presented in Table B34. The weighted average used in the model was calculated on the basis of the number of finished consultant episodes (FCEs) as well as the relevant costs. The resulting value of £616.62 was inflated by 2% to £628.95 in order to reflect current prices.

Table B34: List of relevant HRG codes

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
BZ10D	Minor Orbits or Lacrimal Procedures, 19 years and over, with CC Score 0-1	£613	4,712	NHS SRC 2013
Weighted Average		£616.62		

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

See section 7.5.1 above. NHS reference costs are only appropriate for modelling temporary and permanent punctal occlusion and not the intervention being appraised.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Systematic searches for resource use and costs were undertaken simultaneously with the cost-effectiveness studies. The inclusion criteria are presented in Table B35 below and the search syntax in section **Error! Reference source not found.**.

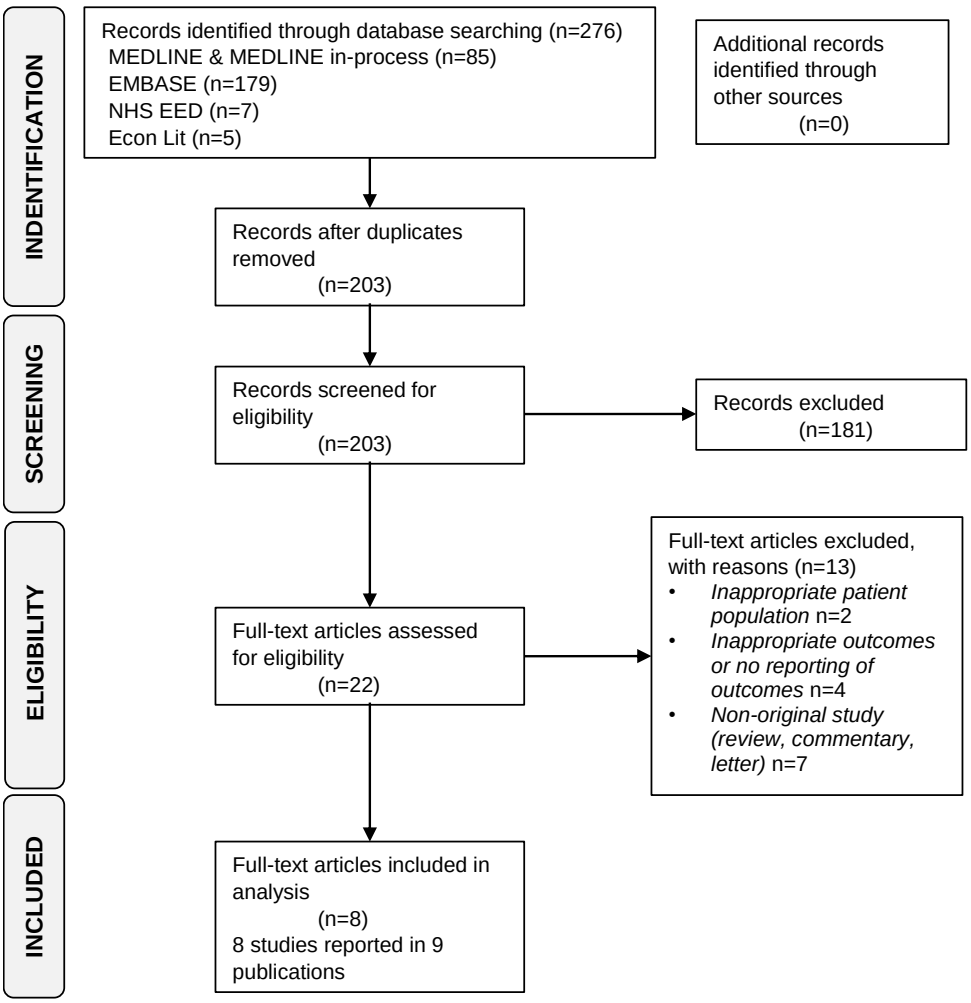


Table B35 Resource use and costs systematic review inclusion criteria

	Inclusion Criteria
Patients	Patients with severe dry eye disease whose disease has not adequately responded to tear substitutes
Subgroups	None
Interventions	Any
Study type	Cost-effectiveness analyses; cost-utility analyses; cost; burden of illness.
Country	UK; France; Germany; Spain; Italy; US
Year of publication	From database inception

Limited economic data are available in the literature for patients with severe DED and no economic information regarding the burden of keratitis within the idiopathic DED population was identified. Only two studies, Clegg (2006) (22) and Yu (2011) (92), reported resource use specifically for people with severe DED, with this group classified based on clinician judgement or on self-reporting, respectively.

The number of clinician visits varied widely by country, possibly reflecting regional differences, or possibly reflecting the panellist method of obtaining data in the reported European countries. Absenteeism attributable to severe DED was considerable. A high use of ocular lubricants was reported in the USA.

Annual costs among people with severe DED were higher than in a general DED population, especially once a societal perspective was considered.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The opinion of clinical experts was not solicited in the assessment of values and hence is not relevant to Ikervis.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The cost of standard therapy is based on four things; the number of eyes treated, the composition of artificial tears, the number of tears used at the start of the therapy, and the absolute number of tears used at the end of the initial six month period of the SANSIKA study. Each of these items is discussed separately below.

Number of eyes treated

By definition, on an individual patient basis the number of eyes treated is either one or two. However, since the model is predicated on a cohort based approach to estimating cost-effectiveness decimal values are feasible. In absence of data we have made the simplifying assumption that the entire cohort has both eyes treated. This approach is justified by the nature of patients recruited into SANSIKA (average number of eyes treated = 1.97) Hence, for the purpose of resource use estimation, the number of eyes treated in the model is set to two.

Composition of artificial tears

The composition of artificial tears was based on a study by Clegg et al. (22), which reported the cost of managing dry eye disease by country and by disease severity. Artificial tear usage for severe dry eye disease patients in the UK is reproduced in Table B36. Note that the numbers do not sum to 100% indicating that patients require, on average, more than one component to treat severe DED.

Due to the severity of the disease, single use preservative free eye drops are recommended to minimize the risk of irritation through the preservatives as

per the NICE clinical knowledge summary. Each single use vial of polyvinyl alcohol and carbomer tears contains sufficient liquid to treat both eyes and can be used at the same time without any additional risk, after use the vial is discarded in accordance with the instructions for use.

Table B36: Composition of standard care (artificial tears) reproduced from Clegg et al. (22)

Treatment option	Value	Source
Polyvinyl alcohol	57%	Clegg et al. (22)
Carbomers	50%	Clegg et al. (22)
Paraffin	50%	Clegg et al. (22)

Baseline artificial tear usage

A key assumption in the model design is that patients recruited into the Ikervis clinical trial program, and in particular into the SANSIKA study, are comparable to individuals with severe DED in the general UK population. As such, the baseline usage of artificial tear usage in the trial can be viewed as reflective of routine care.

The average number of drops per eye per day at baseline in the Ikervis and vehicle arms was 13.24 and 16.54 respectively. While it would have been feasible to use both of these values in the model, we have made the assumption that the differences arose by chance and that it would be better to use a common value for both arms. We have therefore used a simple average of these two values in the model to represent the starting number of drops per eye per day (14.89).

Artificial tear usage at six months

The SANSIKA study reported that artificial tear usage in the Ikervis and vehicle arm at six months (the end of the randomised phase) was 6.34 and 7.32 drops per eye per day respectively. In the context of the decision problem being addressed, and the UK patient population of interest, interpretation of the change from baseline line in the vehicle arm is challenging.

As discussed earlier. Vehicle will not be routinely available in the UK and so any benefits of therapy observed in the trial could again be viewed as either regression to the mean or a placebo effect. In order to align the resource use

component of the model with the approach used to model response to therapy we have chosen to include the benefits observed in the comparator arm in the model. Thus, the average number of average number of drops per eye per day in the standard care arm is set to 14.64 (7.32 drops per eye, 2 eyes treated) and set to 12.68 in the Ikervis arm (6.34 drops per eye, 2 eyes treated).

Artificial tear usage in non-responders

By default, a non-responder (either in the Ikervis or vehicle arm) is assumed to cease therapy and revert back to standard care alone. For these patients we have assumed that artificial tear usage will revert back to baseline and patients in this health state will require 29.78 drops per day (14.89 drops per eye, 2 eyes treated).

Artificial tear usage in other health states

Permanent punctal occlusion is assumed to be 100% successful and as such patients who have this treatment are assumed to no longer require standard care. Hence, artificial tear usage in this state and the post-surgery state is set to zero. During the temporary punctal occlusion trial period, artificial tear usage is also assumed to no longer be required. This can be seen as a very conservative assumption due to tear usage normally only being reduced during the punctual inclusion trial time.

Resource use (Ikervis/ vehicle)

Ikervis is assumed to be used in line with both the SANSIKA trial design and its expected licence, namely one drop per day.

Unit costs used in all AT calculations

Unit costs were taken from the most recent version of the British National Formulary (BNF) (93) at the time of model construction. The values used in the model are presented in Table B37. Each single use vial of polyvinyl alcohol and carbomers is assumed to be able to treat both affected eyes. In order to align the costing with the likely approach used by ophthalmologists in

routine practice, preference has been given to generic rather than branded products.

Table B37: unit costs used in deriving the monthly AT cost

Component	Units per pack	Pack cost	Unit cost	Source
Polyvinyl alcohol[a]	30	£5.35	£0.18	BNF
Carbomers[b]	30	£5.42	£0.18	BNF
Paraffin[c]	1	£3.25	£3.25	BNF

a) Single use Liquifilm Tears® polyvinyl alcohol 1.4%, povidone 0.6%; b) Single use Viscotears® carbomer 980 (polyacrylic acid) 0.2%; c) liquid paraffin 10%, wool fat 10%, in yellow soft paraffin, 4g.

Combining the information in Table B36 and Table B37 with the treatment/ health state specific average number of drops needed yields the monthly AT costs presented in Table B38.

Table B38: Treatment/ health state specific AT costs

Health state	Monthly AT cost
Ikervis + artificial tear usage (induction, response)	£38.67
Artificial tear usage (induction, response)	£44.40
Non-responders	£88.63
Temporary punctal occlusion	£0.00
Permanent punctal occlusion	£0.00
Post-surgery	£0.00

Acquisition cost (Ikervis/ comparator)

A central assumption in the economic evaluation is that Vehicle is an artificial choice of comparator used solely in the Ikervis clinical trial program and not a component of routine clinical practice. In line with this assumption we have made the conservative assumption in all calculations that the acquisition cost of Vehicle is zero. The alternative assumption would have been to assume that the cost of vehicle is the same as one additional tear per eye per day. The acquisition cost of Ikervis has been set to £72 per month.

Summary of all relevant technology costs

A summary of all monthly technology costs is presented in Table B39. Since all therapies are self-administered we have assumed that the costs incurred by the UK NHS of administration, monitoring and additional testing are all zero.

Table B39: Unit costs associated with the technology) in the economic model (per month

Items	Ikervis + AT	AT	Non-responders	Ref in submission
Technology cost	£72	£0	£0	Section 7.5.5
Mean cost of technology treatment	£0	£0	£0	Section 7.5.5
Administration cost	£0	£0	£0	Section 7.5.5
Monitoring cost	£0	£0	£0	Section 7.5.5
Tests	£0	£0	£0	Section 7.5.5
AT usage	£38.67	£44.40	£88.63	Section 7.5.5
Total (per month)	£110.67	£44.40	£88.63	Section 7.5.5

AT: Artificial tears

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

A description of the HRG codes used to model punctal occlusion (both temporary and permanent) is presented in section 7.5.1. The costs associated with the post-surgery state are set to zero due to the assumption of a procedural success rate of 100%. An implication of this assumption is that there will be no need for follow up visits post-surgery. In practice, this assumption is likely to be unrealistic but due to the extremely low procedure rate in the UK the impact on the cost-effectiveness assessment of Ikervis is likely to be negligible.

Treatment with Ikervis has not been assumed to be associated with an improvement in survival. Similarly, we have made the simplifying assumption that the rate of ophthalmologist visits, tests, monitoring etc. will not be affected by either treatment with Ikervis or response status (i.e. we have made the assumption of common resource use across all non-surgical states). As such, the incremental difference between the two arms will be zero. Thus, to keep the model as simple as possible we have not included any such resource use components in the structure.

A summary of the health state costs associated with each health state is presented in Table B40. For presentational purposes, we have listed the one-off procedure costs as a separate line item.

Table B40: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
Ikervis + artificial tear responder costs	Technology	£110.67	Section 7.5.6
	Staff	£0	
	Hospital costs	£0	
	Procedure cost	£0	
	Total	£110.67	
Artificial tears responder costs	Technology	£44.40	Section 7.5.6
	Staff	£0	
	Hospital costs	£0	
	Procedure cost	£0	
	Total	£44.40	
Non-responder (all interventions)	Technology	£88.63	Section 7.5.6
	Staff	£0	
	Hospital costs	£0	
	Procedure cost	£0	
	Total	£88.63	
Punctal plugs	Technology	£0	
	Staff	£0	
	Hospital costs	£0	
	Procedure cost	£628.95	Section 7.5.1
	Total	£628.95	
Permanent punctal occlusion	Technology	£0	
	Staff	£0	
	Hospital costs	£0	
	Procedure cost	£628.95	Section 7.5.1
	Total	£628.95	
Post-surgery	Technology	£0	
	Staff	£0	
	Hospital costs	£0	
	Procedure cost	£0	
	Total	£0	Section 7.5.6

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Treatment emergent adverse effects associated with Ikervis were not modelled and hence have no cost. See section 7.3.1. Punctal occlusion is low-risk and given the very low procedure rates in the UK, the incremental cost of treat of procedure related adverse events will be negligible. As such, these have also not been included in the model structure.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs have been included in the model.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Utility values for response and non-response derived using alternative elicitation techniques were sought from the literature and applied to assess the robustness of the results to changes in the base case values. The alternative scenario investigated used utilities from Schiffman et al. (26) of 0.72 for non-responders and 0.78 for responders. See section 7.4.9 for more details.

One of the key structural assumptions of the model was around the treatment continuation probability for individuals receiving artificial tears alone after the initial trial period (i.e. in the comparator arm). In the absence of data, the model assumed a dropout rate equal to that seen in the first 6 months of the trial (see section 7.3.1 for more details). To analyse the effect of this assumption on the cost-effectiveness of Ikervis, we explored the alternative assumption of equivalent long term cessation rates in both arms of the model.

Other structural assumptions assessed include:

- The use of utilities derived using the SANSIKA primary endpoint

- Truncation of the model time horizon
- Altering the number of eyes treated)
- Three month trial period for Ikervis and artificial tears

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Table B41 summarises the variables included in the univariate deterministic sensitivity analysis. Where standard errors were reported a range of +/- two standard errors from the mean was used to inform the upper and lower values used in the analysis. When no such information was available and arbitrary range of +/-20% was used to create the range used in the deterministic analyses. Parameters which were assumed to have a base case value of zero value were assigned arbitrary upper limits to test the validity of the assumption.

Table B41 Deterministic sensitivity analysis

Parameter	Base case value	Lower limit	Upper limit
3 month response probability (Ikervis)	0.162	0.13	0.194
6 month response probability (Ikervis)	0.188	0.15	0.226
3 month response probability (AT)	0.077	0.061	0.093
6 month response probability (AT)	0.077	0.061	0.093
No response to temporary plugs	0.0024	0.00192	0.0029
Temporary plugs to permanent plugs	0.1	0.08	0.12
Treatment failure (Ikervis)	0.109	0.087	0.138
Treatment failure (AT)	0.122	0.0976	0.1464
Ikervis acquisition cost	£72	£50	£100
Ikervis total cost	£110.67	£88.53	£132.80
Vehicle acquisition cost	£0	£0	£5
AT total cost	£44.40	£35.52	£53.28
Non-responders AT cost	£88.63	£70.90	£106.35
Temporary plugs cost	£628.95	£503.16	£754.74
Permanent plugs cost	£628.95	£503.16	£754.74
Post-surgery cost	£0	£0	£100
Polyvinyl alcohol pack cost	£5.35	£4.28	£6.42
Carbomers pack cost	£5.42	£4.28	£6.50
Paraffin cost	£3.25	£2.60	£3.90
Background AT cost (AT)	£44.40	£35.52	£53.28
Background AT cost (Ikervis)	£38.67	£30.94	£46.04
Background AT cost (temporary plugs)	£0	£0	£10
Background AT cost (permanent plugs)	£0	£0	£10
Background AT cost (non-responders)	£88.63	£70.90	£106.36
AT drops per day	14.64	11.712	17.568
Ikervis drops per day	12.68	10.144	15.216
Temporary plugs drops per day	0	0	10
Permanent plugs drops per day	0	0	10
Non-responders drops per day	29.78	23.824	35.736
Drops per eye per day	2	1	2
Drops per eye per day (temporary plugs)	2	1	2
Drops per eye per day (permanent plugs)	2	1	2
No response utility	0.66	0.656	0.664
Response Utility	0.738	0.669	0.806

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A full probabilistic sensitivity analysis was undertaken. The parameters included and their chosen distributions are detailed in Table B42. Standard error estimates of 10% of the mean value were used unless reported.

Table B42 Parameters included in PSA

Parameter	Distribution	Justification for distribution
	Costs	
Temporary punctal plug cost	Gamma	Required value in range [0,∞) and right skewed
Permanent punctal plug cost	Gamma	Required value in range [0,∞) and right skewed
Post-surgery cost	Gamma	Required value in range [0,∞) and right skewed
	Usage	
Number of eyes treated	Beta	Required value in range [0,1]
Polyvinyl alcohol	Beta	Required value in range [0,1]
Carbomers	Beta	Required value in range [0,1]
Paraffin	Beta	Required value in range [0,1]
	Utilities	
No response	Beta	Required value in range [0,1]
Improvement in utility with response	Beta	Required value in range [0,1]
	Transition probabilities	
Ikervis + AT trial to Ikervis + AT maintenance (months 0-3)	Beta	Required value in range [0,1]
Ikervis + AT trial to Ikervis + AT maintenance (months 0-6)	Beta	Required value in range [0,1]
AT trial to AT maintenance (months 0-3)	Beta	Required value in range [0,1]
AT trial to AT maintenance (months 0-6)	Beta	Required value in range [0,1]
Non-responders to temporary punctual plugs	Beta	Required value in range [0,1]
Temporary to permanent punctal plugs	Beta	Required value in range [0,1]
	Treatment failure probabilities	
Ikervis + AT Failure Probability	Beta	Required value in range [0,1]
AT (no ciclo) Failure Probability	Beta	Required value in range [0,1]

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Aggregate utility gains in a responder

Input data can be used to calculate the aggregate utility gain associated with ikervis therapy. Using the post hoc definition of response (see section 6.3.7), the difference in utility for patients in the ikervis plus AT arm compared to baseline is +0.02 (18.8% of patients responded, gain in utility for responders = 0.08). Using the SANSIKA primary outcome measure definition the impact of therapy on utility was +0.03 (32.8% of patients responded, gain in utility for responders = 0.08).

Whilst it is challenging to provide context to utility gains, Schiffman et al. (26) conducted a TTO study in patients with DED and reported a utility of 0.72 in patients with severe dry eye and 0.78 in those with asymptomatic or moderate dry eye, leading to a potential utility gain of 0.06. In addition, a previously published cost-effectiveness analysis of 0.05% ciclosporin using these utilites reported gains of 0.02 and 0.05 for vehicle and ciclosporin over no treatment for a moderate to severe DED population. (82)

Aggregate time on treatment

Based on all input values, using the post-hoc definition of response, the expected time on Ikervis therapy is 15.4 months. Using the SANSIKA primary outcome definition of response this value increases to 22.5 months. Of note, both of these estimates included an enforced period of six months (as per the SANSIKA protocol which may not be reflective of routine clinical practice. Clegg et al. (22) reported that the average time on treatment can be up to 52 weeks with previous treatment options.

Previous studies

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Cycle and treatment specific proportions of patients in each health state are reproduced from the economic model in section 9.14.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Cycle and treatment specific estimates of cumulative QALY gains are reproduced from the economic model in.section 9.15.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

A breakdown of the required outputs, by core health state (i.e. expected lifetime per-patient values stratified by responder/ non-responder) is presented in Table B43 below. For convenience, we have also included the predicted per-patient cost incurred by the UK NHS by response category and treatment modality. A breakdown of the total per-patient lifetime expected costs is presented in Table B44.

Table B43: Model outputs by clinical outcomes (post-hoc response definition)

Outcome	LY	QALY	Cost (£)
	AT alone		
Responder	1.00	0.34	402
Non-responder	13.86	9.37	14,882
Overall survival	14.85	9.71	15,283
	Ikervis +AT		
Responder	1.42	0.69	1,582
Non-responder	13.43	9.05	14,414
Overall survival	14.85	9.74	15,997

LY, life years; QALY, quality-adjusted life year

Table B44: Predicted resource use by cost category (post-hoc response definition)

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

* Due to rounding, the incremental cost for non-responders is out by £1 (unrounded costs for Ikervis + AT of £21,406.22 and for AT alone; £21,949.69)

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

N/A. the relevant values are presented in Table B43 and Table B44 above.

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The per-patient lifetime costs and benefits of each therapy, as well as incremental values are presented in Table B45. Compared to standard tears alone, the inclusion of ikervis results in a lifetime cost to the UK NHS of £713 per patient but offers and additional 0.04 QALYs. The ICER is therefore £19,156 per QALY gained.

Table B45: Deterministic base-case results (post-hoc response definition)

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
AT alone	£15,283	9.71			
Ikervis + AT	£15,997	9.74	£713	0.037	£19,156

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The effect of parameter uncertainty on model estimates in order of importance is presented in Table B46 with the 10 most influential parameters included in a tornado diagram in Figure B11.

Table B46 Deterministic sensitivity analysis (£/QALY gained, post-hoc response definition)

Parameter	Low value	High value
Response Utility set to 0.67/0.81	£165,654	£10,166
Ikervis acquisition cost set to £50/£100	£10,709	£29,906
Ikervis total health state cost set to £88.6/£132.8	£10,693	£27,651
6 month response probability (Ikervis) set to 0.15/0.23	£26,318	£15,381
Non-responders AT cost set to £70.9/£106.4	£21,623	£14,792
Drops per eye per day set to ½	£23,291	£19,156
Treatment failure (Ikervis) set to 0.087/0.131	£15,700	£23,042
6 month response probability (AT) set to 0.061/0.093	£16,411	£22,648
Treatment failure (AT) set to 0.098/0.146	£22,303	£17,305
Background AT cost (Ikervis) set to £30.9/£46.0	£16,187	£21,984
Ikervis drops per day set to 10.14/15.22	£16,311	£22,001
Background AT cost (non-responders) set to £370.9/£106.4	£21,623	£16,690
Non-responders drops per day set to 23.82/35.74	£21,577	£16,735
AT total cost set to £35.5/£53.3	£21,312	£16,999
Background AT cost (AT) set to £35.5/£53.3	£21,312	£16,999
AT drops per day set to 11.71/17.57	£21,233	£17,078
Vehicle acquisition cost set to £0.0/£5.0	£19,156	£17,942
No response utility set to 0.65/0.66	£18,128	£20,308
Polyvinyl alcohol pack cost set to £4.3/£6.4	£20,032	£18,280
Carbomers pack cost set to £4.3/£6.5	£19,931	£18,380
3 month response probability (Ikervis) set to 0.13/0.19	£19,480	£18,848
Post-surgery cost set to £0.0/£100.0	£19,156	£18,996
3 month response probability (AT) set to 0.061/0.093	£18,999	£19,315
Temporary plugs to permanent plugs set to 0.080/0.120	£19,091	£19,221
Temporary plugs cost set to £503.2/£754.7	£19,197	£19,117
No response to temporary plugs set to 0.002/0.093	£19,117	£19,194
Temporary plugs drops per day set to 0/10	£19,156	£19,146
Permanent plugs cost set to £503.2/£754.1	£19,160	£19,152
Background AT cost (temporary plugs) set to £0.0/£10.0	£19,156	£19,153
Permanent plugs drops per day set to 0/10	£19,156	£19,155
Paraffin cost set to £2.6/£3.9	£19,155	£19,156
Background AT cost (permanent plugs) set to £0.0/£10.0	£19,156	£19,155
Drops per eye per day (temporary plugs) set to 1/2	£19,156	£19,156
Drops per eye per day (permanent plugs) set to 1/2	£19,156	£19,156

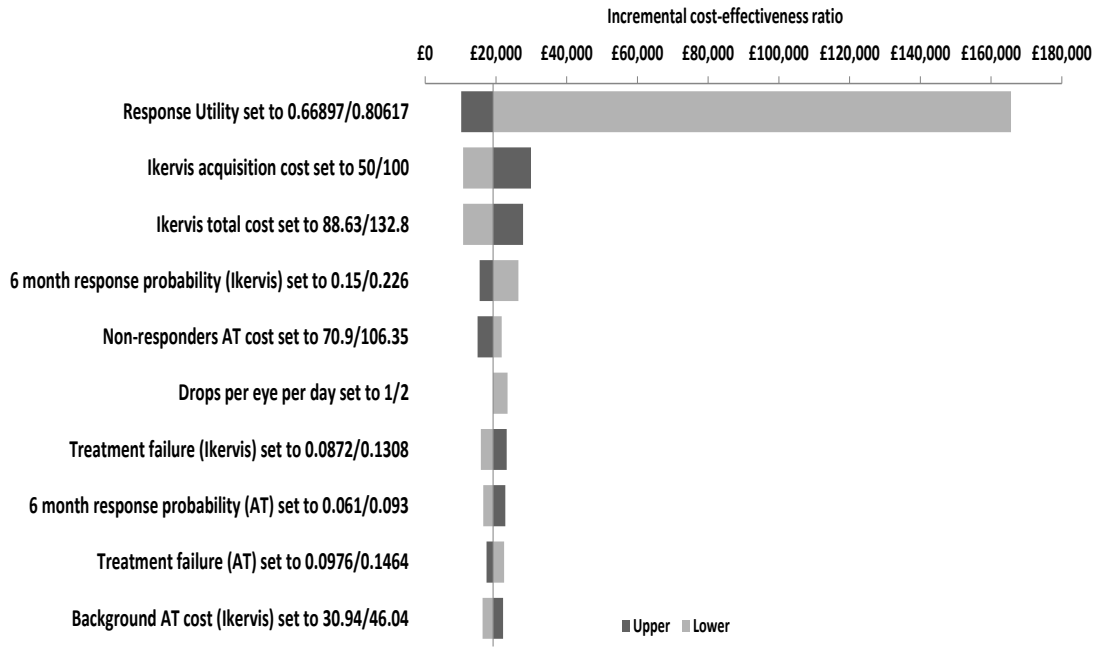


Figure B11 - Deterministic sensitivity analysis - Tornado diagram

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results from the probabilistic sensitivity analysis are presented in Table B47 with values corresponding to the mean and 95% credible interval (CrI) from 1,000 model simulations. The probabilistic ICER is £18,835 per QALY gained (95% CrI £8,042 to £90,799).

Table B47: Probabilistic base-case results (post-hoc response definition)

	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER (per QALY gained)
AT alone	£16,014 (14,027 to 17,925)	9.71 (9.64 to 9.79)			
Ikervis+AT	£15,287 (13,217 to 17,258)	9.75 (9.66 to 9.85)	£726 (624 to 855)	0.04 (0.01 to 0.10)	£18,835 (8,042 to 90,799)

The cost-effectiveness plane arising from the probabilistic analysis is presented in Figure B12 and the associated cost-effectiveness acceptability curves in Figure B13. Ikervis offered additional benefit in every simulation run and at a cost-effectiveness threshold of £20,000 per QALY gained the probability that Ikervis is cost-effective is 46.4%. At a threshold value of £30,000 per QALY gained, this probability increases to 70.8%.

However, a number of the simulation generated incremental benefits very close to zero meaning that the probabilistic results (especially the credible intervals around the ICER) are unstable and should be interpreted with caution.

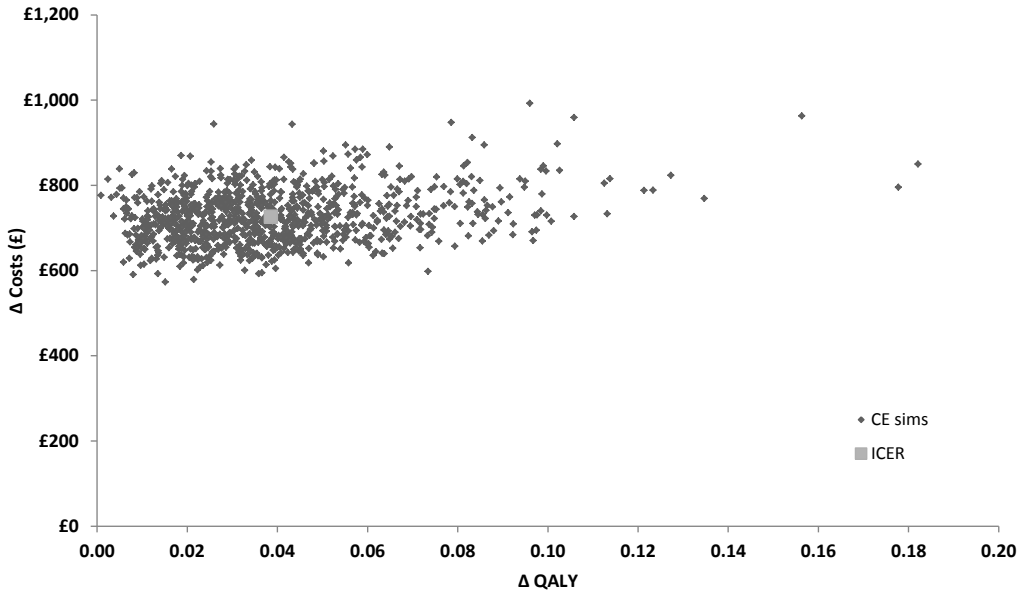


Figure B12 Cost-effectiveness plane

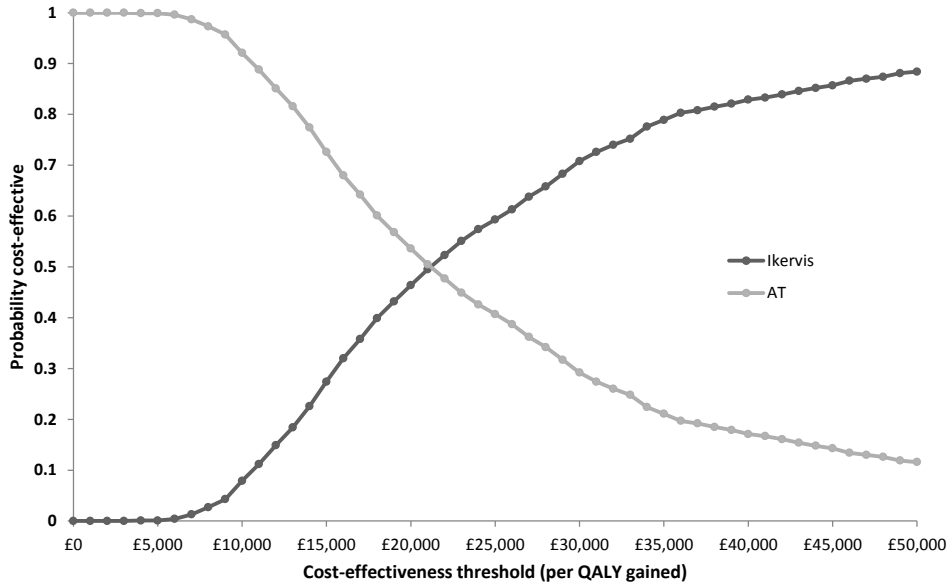


Figure B13 Cost-effectiveness acceptability curve (CEAC)

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Primary endpoint improvement criteria (CFS ≥ 2, OSDI ≥ 30%)

Cost-effectiveness results using the response definition corresponding to the primary outcome measure from the SANSIKA study are presented in Table B48. Compared to the base case, Ikervis has slightly higher incremental costs and slightly lower incremental QALYs. However, the incremental benefits remain small and so the model is sensitive to changes in cost; small absolute changes in costs can result in a large absolute change in the ICER.

Table B48 Primary endpoint cost-effectiveness results

	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER (per QALY gained)
AT (no cyclosporine)	£14,987	9.754			
Ikervis + AT	£16,132	9.788	£1,145	0.034	£33,291 per QALY

Alternative approaches to deriving response stratified utility values.

In line with the NICE reference case, we have used utility data elicited directly using the EQ-5D instrument in the base case analysis. However, our literature review identified other sources of health state preference weight data, in particular a study by Schiffman et al (26) who elicited values using a TTO based approach. While not compliant with the NICE reference case, we have used the information from this paper to inform a sensitivity analysis around utility estimates, the results of which are presented in Table B49. Again, there are very small absolute changes to the absolute values but the ICER increases to approximately £24,800 per QALY gained.

Table B49 Alternative utilities cost-effectiveness results

	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER (per QALY gained)
AT (no cyclosporine)	£15,283	10.578			
Ikervis + AT	£15,997	10.607	£713	0.029	£24,765 per QALY

Alternative utilities of responders to treatment

As noted in Figure B11, the parameter where uncertainty has the greatest effect on the model is the utility associated with responders to treatment. Against a baseline utility of 0.66 for non-responders to treatment, Figure B14 presents graphically the ICER of Ikervis with a range of alternative response

utilities. It was found that Ikervis becomes cost-effective at a threshold of £30,000 per QALY gained at utilities around 0.71 (i.e. an incremental gain for responders of 0.05).

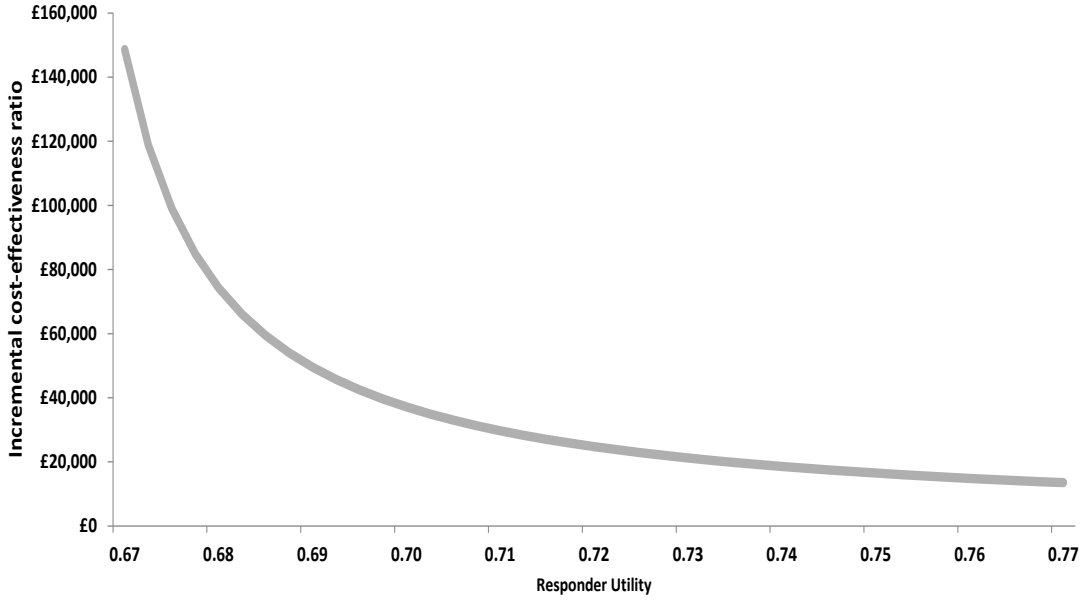


Figure B14 Cost-effectiveness at alternative response utilities

Three month trial period

As noted in section 7.3.1, the majority of patients who respond to both Ikervis and artificial tears are identified within the first three months. Truncating the initial trial period has the potential of reducing costs of patients between three and six months who are not responsive to treatment. Cost-effectiveness results of this scenario analysis are presented in Table B50.

Table B50 Three month trial period - cost-effectiveness results

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
AT alone (6 month trial)	£15,283	9.71			
Ikervis + AT (6 month trial)	£15,997	9.74	£713	0.037	£19,156
AT alone (3 month trial)	£15,414	9.70			
Ikervis + AT (3 month trial)	£15,911	9.73	£496	0.026	£18,739

Time Horizon

Cost-effectiveness results with shorter time horizons are detailed in Figure B15. The model is insensitive to time horizons longer than 10 years.

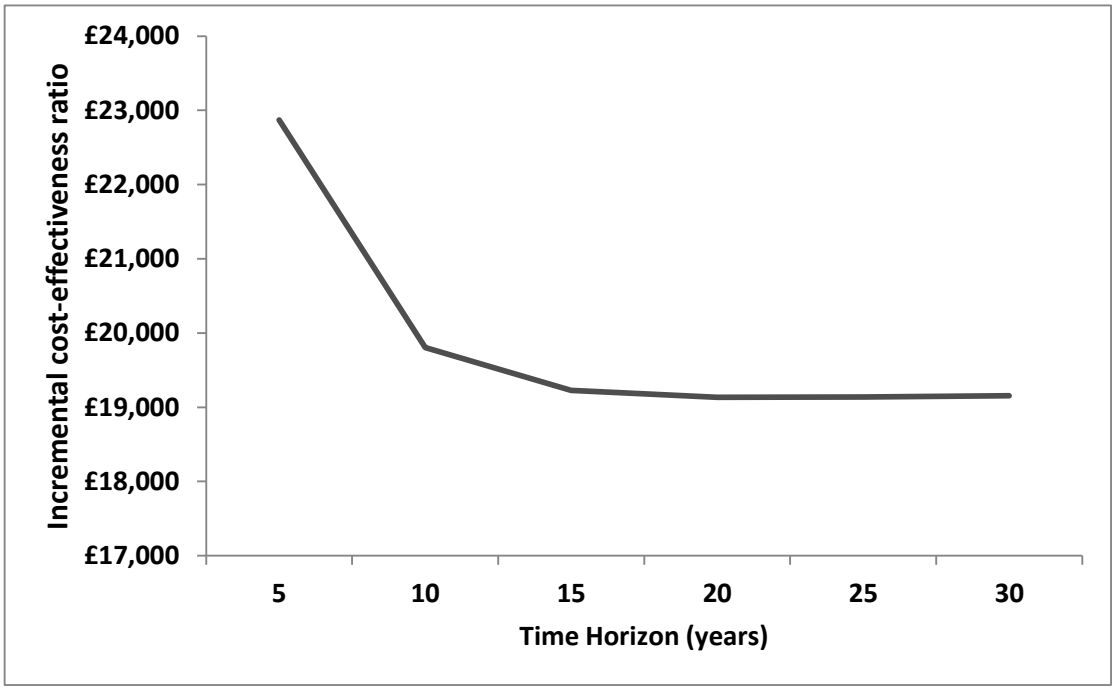


Figure B15 Cost-effectiveness of Ikervis with alternative time horizons

Number of affected eyes

Cost-effectiveness results for Ikervis when the mean number of eyes treated in each patient is altered across a range of all possible values are presented in Figure B16. A linear relationship is observed with the cost-effectiveness of Ikervis decreasing from a maximum of £19,156 per QALY when both eyes are treated to a minimum of £23,290 per QALY when only one eye is treated.

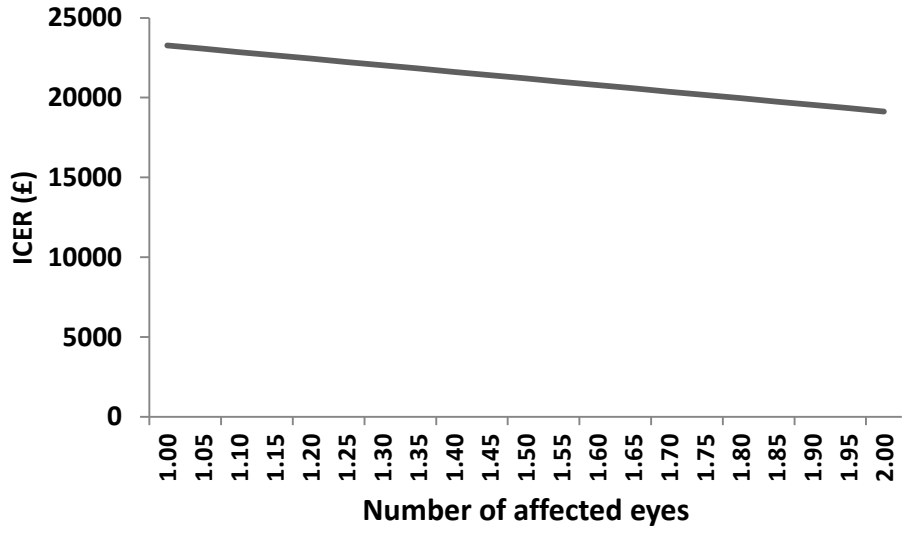


Figure B16 Cost-effectiveness of Ikervis with alternative numbers of eyes treated

7.7.10 What were the main findings of each of the sensitivity analyses?

Probabilistic sensitivity analysis confirms that Ikervis produces a benefit to patients, generating a utility gain compared artificial tears without cyclosporine in all 1000 simulations. Lifetime costs increased in every simulation, typically between £600 and £1000 per patient using the post-hoc definition of response from the SANSIKA study. At a cost-effectiveness threshold of £20,000 per QALY, Ikervis is cost-effective in around 46% of simulations, a figure which increases to 71% at £30,000 per QALY. The probabilistic ICER of Ikervis is £18,835; the corresponding deterministic ICER is approximately £19,200 per QALY gained.

Using the SANSIKA primary endpoint definition of response, a greater percentage of patients are classified as responders in both arms of the model. Although treatment with Ikervis is associated with a lower rate of artificial tear usage, the additional cost of Ikervis leads to an increased monthly cost over non-responders to treatment. Responders to artificial tears have a lower rate of tear usage than non-responders and hence a lower cost. Therefore higher response rates, particularly in the comparator arm when the primary endpoint response definition is used have the effect of increasing the ICER to around £33,000 per QALY.

Univariate deterministic sensitivity analysis identified the absolute utility value for a treatment responder (however defined) as the parameter that had the greatest impact on cost-effectiveness. In practice, this can be thought of as being synonymous with the incremental benefit on HRQoL associated with responding to therapy compared to non-response. Since the use of Ikervis is associated with a higher probability of a positive response, a greater incremental utility gain results in a greater differential utility and a lower ICER. We performed a threshold value to identify the magnitude of responder utility benefit that would be required to result in Ikervis being cost-effective at a threshold of £30,000 per QALY gained (Figure B14). The corresponding cut-

off value was approximately 0.05, a smaller value than that observed in both SANSIKA and published literature. (26) (27)

Absolute utilities in Schiffman 2003 (26) (0.78 for responders and 0.72 for non-responders) are slightly higher than those in the SANSIKA trial. The incremental utility gain of 0.06 is also marginally smaller the 0.078 used as base case in the model. When these alternative values are used in the model the incremental lifetime costs remain unchanged but the incremental lifetime QALY gain decreases from 0.037 to 0.029. This change results in the ICER increasing to approximately £24,800 per QALY gained. Of note, is that these results were generated using a TTO based approach which is not in line with the NICE reference case.

Using a three month rather than a six month trial period for Ikervis has a modest effect on cost-effectiveness. Incremental costs reduce by £217 per patient and incremental QALYs gained fall by 0.09. This has the effect of reducing the overall ICER by £417 per QALY gained to £18,739.

The model was modestly sensitive to the choice of time horizon, with a truncation of the number of cycles having a limited effect on the ICER. The model is robust to time horizons greater than 10 years and a significant impact on ICERs is only observed when horizons are shortened to around one year. This is because much of the benefit of Ikervis comes from a higher response rate post-treatment. When time horizons are constrained the additional benefit of a higher response rate occurs over a much shorter period, lessoning the incremental benefit of Ikervis. By 10 years, the vast majority are no longer expected to be on treatment and the model becomes essentially homogenous. A 30 year time horizon is therefore sufficient to capture all of the benefits and costs associated with treatment.

In the base case model, everybody who requires treatment is assumed to require treatment in both eyes, with the justification for this assumption being the baseline characteristics of patients recruited into SANSIKA and clinical opinion. However, if each patient is assumed to have only one treated eye rather than two, the ICER increase from £19,500 to £23,300 per QALY

gained. Given the robustness of this assumption, and in particular it's high alignment to routine clinical practice in patients with severe DED who have not adequately responded to tear substitutes, this result is likely to be solely of theoretical rather than practical relevance.

7.7.11 What are the key drivers of the cost-effectiveness results?

As discussed in 7.7.10, and described graphically in Figure B11, the most sensitive parameter of the model is the utility estimate of patients who respond positively to treatment. With low incremental utilities of response, Ikervis becomes increasingly less cost-effective; however there is strong evidence to support the assertion of at least the 0.05 utility gain of response required for Ikervis to be cost-effective.

Another key driver of the cost-effectiveness results is the cost of Ikervis. This is perhaps unsurprising because in the absence of adverse events, the key differentiator between the two arms of the model in terms of costs is the acquisition cost of Ikervis. If Ikervis were to cost £50 per month, incremental costs decrease to £399 and the corresponding ICER falls to £10,709 per QALY gained.

Further drivers of the cost-effectiveness results are the response probabilities of Ikervis and vehicle at 6 months and also their treatment failure rates. Both parameters are used to estimate the number of patients on treatment over time and hence any changes in these parameters are extrapolated over an extended time horizon. However, when the most sensitive of these parameters – Ikervis response probability – is increased to its upper limit, ICERs still only increase to £26,318 per QALY.

The model was found to be robust to a number of other parameters including the cost of temporary and permanent punctal plugs, 3 month response probabilities to both treatments and the costs of the individual components of artificial tears.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The conceptual model structure has also been reviewed and approved by clinicans familiar with the underlying condition. The model has also undergone rigorous technical validation by senior modelers not involved in the original model construction.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

The analysis of population subgroups was not undertaken as part of this analysis.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Patients with Sjogren's syndrome are a potential subgroup which could have been considered. However analysis based on this population subset was not included because the SANSIKA trial was not powered to assess the benefit of Ikervis to these patients. Any inference would therefore require the use of published literature in different patient groups or clinical input which would have added to the uncertainty of the model.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No published literature was identified and hence a cross-validation of the model results is not possible.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes, the model results relates to all patients who meet the wording of the NICE scope.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The model is based, where possible on information from a large, multi-national randomised, double-blind clinical trial. Where information was not available from this study we have tried to use publically available information (either from other randomised studies identified via a formal systematic review or from national databases). The modelling approach is also fully compliant with the NICE reference case. Full and extensive sensitivity analyses were

also conducted. As such, the approach is a robust attempt to synthesise all available information in a single, robust framework.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As the model was most sensitive to the utility gain associated with treatment response and so further, collaboratory information for this parameter would be most useful.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

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. (94)

There is ample evidence that female sex and postmenopausal estrogen therapy are important risk factors for dry eye.(1, 36, 95) Mathers et al. also showed significant age-related correlations for tear evaporation, volume, flow, and osmolarity.(96) Aging is associated with physiological changes that may predispose to dry eye, including decreased tear volume and flow, increased osmolarity, decreased tear film stability, and alterations in the composition of the meibomian lipids. (96-98).

The estimate provided, takes into account the distribution of sex and age in the population for England and Wales. Therefore, the prevalence of dry eye disease was estimated by leveraging the findings of three studies that targeted specific brackets of age and sex. Schaumberg et al. in 2003

assessed prevalence in men over 50 years of age, and in 2009 in women over 50 years of age. In order to model the prevalence in the population under the age of 50, the study by Clegg et al. was used. (22, 36, 37)

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.(23) The estimate of the share of severe patients was therefore taken from a research on severe dry eye disease done in ophthalmologists (Santen data on file, 2013), assessing the treating physicians' perception of the prevalence of severe patients. In this study, ophthalmologists indicated that 6% of their dry eye patients would suffer from severe dry eye disease with marked symptoms and corneal alterations. It is assumed, conservatively that 100% of the severe DED population would have keratitis and be eligible for treatment.

The confirmed size of the English and Welsh adult population (18-90 yr.) in mid-2013 was 44,811,567. Based on this it is estimated that 61,302 people had severe dry eye with keratitis and were treated. Epidemiology data for people with severe DED is extremely limited. This population size was estimated by assuming that DED has a prevalence of 2.28% in the general population and of DED patients 6% are assumed to have severe DED.

	Prevalence DED	**DED patients with severe disease**	**Severe DED with keratitis**	**Severe DED with keratitis, diagnosed and treated**
	2.28%	6.00%	100.00%	100.00%
Number	1,021,704	61,302	61,302	61,302

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

There are currently no licensed treatments for people with severe DED and keratitis. Assumptions regarding treatment in this population are outlined in section 2.7. It has been assumed that in 2015 3% of people eligible for

Ikervis® will start treatment. This will increase to 33% of eligible patients over five years (assuming that eligible patients will reduce to 85% of the total severe DED with keratitis population based on people stopping treatment when response to treatment stops). Two alternative levels of uptake have been demonstrated where a higher level of uptake has been assumed resulting in, after five years of availability, 77% or 88% of the eligible population are receiving treatment. We present the 33% of the population receiving Ikervis® as the conservative base case.

8.3 What assumption(s) were made about market share (when relevant)?

In the first year of Ikervis® availability it has been assumed that 100% of people with severe DED and keratitis that are diagnosed and treated will be eligible for Ikervis®. Of the eligible population 3% will receive treatment. As the Ikervis® clinical trial programme has demonstrated, response to treatment will not last. Once treatment stops being effective the individual will stop treatment and start a new treatment. It has been assumed that over the first three years of availability people eligible for Ikervis® will drop to 85% of the total severe DED and keratitis population. Although the eligible population will reduce the market share within this population will increase to 33% after five years. The anticipated market share and number of people receiving Ikervis® is outlined below.

Financial year	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
Eligible for Ikervis®	100%	90%	90%	85%	85%	85%
uptake #1	3%	10%	16%	20%	26%	33%
update #2	10%	24%	36%	52%	66%	77%
update #3	16%	35%	59%	74%	83%	88%
Patients receiving Ikervis®						
uptake #1	1,839	5,517	8,828	10,421	13,548	17,195
update #2	6,130	13,241	19,862	27,096	34,391	40,122
update #3	9,808	19,310	32,551	38,559	43,249	45,854

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to

commissioners (for example, procedure codes and programme budget planning).

Not applicable.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

See section 7.5.

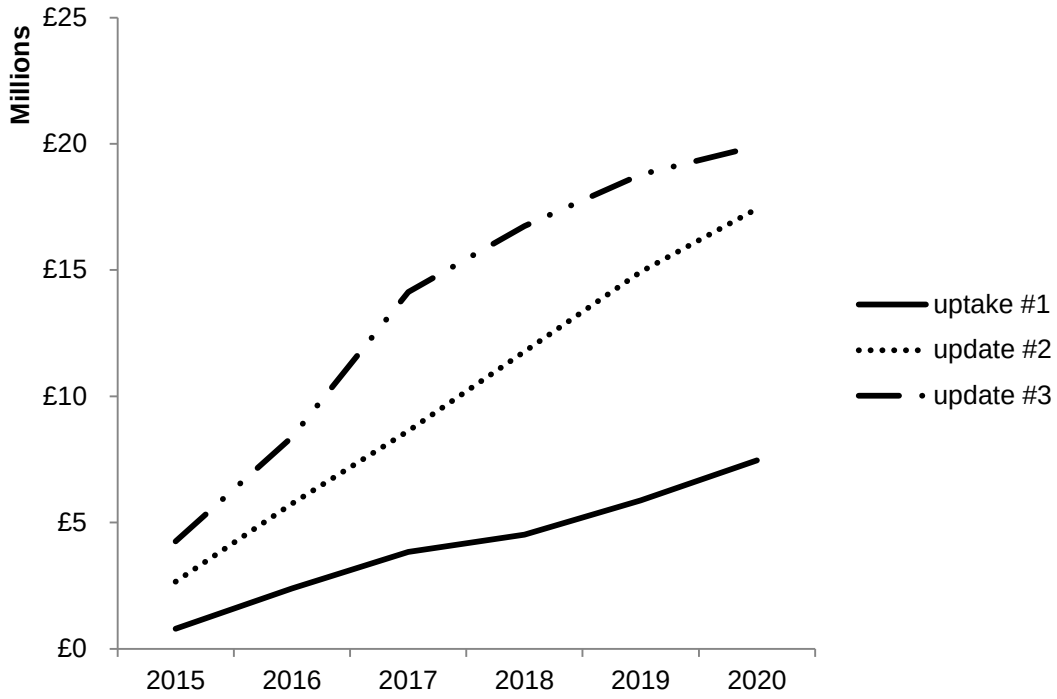
8.6 Were there any estimates of resource savings? If so, what were they?

Responders to Ikervis® demonstrate a reduction in the use of concomitant artificial tears. See section xxx for more detail.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

In 2015, the estimated annual budget impact in England and Wales is £798,688, corresponding to £434 per individual with severe DED and keratitis. Budget impact over five years is presented below:

	2015	2016	2017	2018	2019	2020
Annual budget impact						
uptake #1	£798,688	£2,396,065	£3,833,704	£4,525,900	£5,883,670	£7,467,735
update #2	£2,662,294	£5,750,556	£8,625,833	£11,767,341	£14,935,471	£17,424,716
update #3	£4,259,671	£8,386,227	£14,136,783	£16,745,831	£18,782,486	£19,913,961



8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable.

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Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched:

- Medline® and Medline® In-process (OVID SP)
- Embase (OVID SP)
- CENTRAL (Cochrane Library)
- PubMed

9.2.2 The date on which the search was conducted.

Searches were conducted on 21st July 2014.

9.2.3 The date span of the search.

Searches were conducted from database inception (Medline® 1946; Embase 1947; CENTRAL 1898) to 21st July 2014. The search in PubMed was limited to identify E-publications ahead of print.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp Dry Eye Syndromes/ (14368)
2 (dry eye adj3 (syndrome*1 or disease*1)).ti,ab. (1493)
3 keratoconjunctivitis.ti,ab. (3658)
4 sjogren*2.ti,ab. (11907)
5 xerophthalmia.ti,ab. (766)
6 (dysfunctional tear adj3 (syndrome*1 or disease*1)).ti,ab. (27)
7 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae).ti,ab. (111)
8 or/1-7 (21296)
9 Anti-Inflammatory Agents/ (56104)
10 cyclosporine/ (26117)
11 (c#closporin* or cylcokat or ikervis or cipol or deximune or implanta or imusporin or vekacia or neoral or restasis or sandim* or adi 628 or adi628 or cicloral or consupren or equoral or gengraf or ol 27400 or ol27400 or pulminiq or sang 35 or sang35 or sangcya).mp. (52118)
12 Adrenal Cortex Hormones/ (52737)
13 steroid*.mp. (267842)
14 (loteprednol etabonate or alrex or cddd 5604 or cddd5604 or "chloromethyl 17alpha ethoxycarbonyloxy 11beta hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate" or hgp 1 or hgp1 or lotemax or loter#x or lotesoft or p 5604 or p5604).mp. (126)
15 fluorometholone/ (251)
16 (fluorometholone or "21 desoxy 6alpha methyl 9alpha fluoroprednisolone" or "21 desoxy 9alpha fluoro 6alpha methylprednisolone" or "9alpha fluoro 11beta,17alpha dihydroxy 6 alpha methylpregna 1,4 diene 3,20 dione" or cortilet or delmeson*1 or efflumidex or eflone or flosef or fluaton or flucon or fluforte liquifilm or flulon or flumelon or flumetholon* or flumex* or

flumetholone or fluoph or fluro op or fluorlon or flurometholon or fluoromethalone or fluoropos or fuluson or isopto flucon or loticort or methasite or oxylone).mp. (359)

17 methylprednisolone/ (16049)

18 (methylprednisolone or "11beta,17alpha,21 trihydroxy 6 alpha methyl 1,4 pregnadiene 3,20 dione" or "6 methyl delta 1 hydrocortisone" or "6alpha methyl delta1 hydrocortisone" or adlone* or dep medalone or depmedalone or depoject or depopred or esametone or firmacort or medixon or mednin or medralone or medrate or medrol or medrone or medprednisolone or mesopren or methacort or methyl prednisolone or methylcotol* or methylpred or methylsterolone or metidrol or metrisone or metycortin or metypred or metypresol or neomedrone or nsc 19987 or nsc19987 or prednol or solomet or solu decortin or urbason).mp. (21688)

19 ((occlu* or plug*) adj2 puncta*).ti,ab. (292)

20 ((lacrimal or puncta*) adj2 occlus*).ti,ab. (185)

21 Serum/ (5204)

22 (autologous adj2 serum*).ti,ab. (1814)

23 Ophthalmic Solutions/ (11361)

24 (eye adj2 (drop*1 or instill*)).ti,ab. (3970)

25 (eyedrop*1 or opthalmic solution*1).ti,ab. (1842)

26 acetylcysteine/ (10272)

27 (acetylcysteine or acetyl cysteine or acetyl l cysteine or acerac or acetadote or acetain or acypront or acys 5 or airbron or alveolex or bromuc or brunac or cetilan or drenaflen or ecomucyl or encore or exomuc or fabrol or flemex ac or fluim#cil or fluimukan or fluprowit or flutafin or hidonac or inspir or alpha acetamido beta mercaptopropionic acid or lappe or libramucil or "m.c.t." or menaxol or mercapturic acid or mucocil or mucofillin or mucolator or mucomiste or mucomyst or mucopect or mucoserin or mucosil or mucosof or mucosol or mucosolvin or mucosten or mucoza or mukolit or muteran or nsc111180 or nsc 111180 or parvolex or reolin or respaire or sigamucil or siran 200 or siran200 or solmucol or spatam or sputoprompt or stecin or tixair or zifluvis).mp. (21884)

28 (adatocel or artelac or atract or cellugel or celulose grin or contactol or genteal or gonak or goniosoft or goniosol or hyroxypropyl methyl cellulose or hyroxypropyl methylcellulose or hydroxypropylmethyl cellulose or hypromellose or isopto* or k 8515 or k8515 or lac oph or lacrisic or lacrisifi or lubafax or methocel or methopt or methylhydroxypropyl cellulose or methylhydroxypropylcellulose or metolose or naturalag or nicotears or nova vizol or occucoat or ocucoat or opsil tears or oq coat or pharmacoat or sic opthal or tears natural ii or ultratears).mp. (1809)

29 Carboxymethylcellulose Sodium/ (2045)

30 (carboxymethylcellulose or almelose or apergel or blandlax or bu lax or carbethox or carbose d or carboxy methyl cellulose or carboxymethyl cellulose or carboxy methyl cellulose or carmellose or carmethose or cel o brandt or cellofa* or cellufresh or cellulose gum or

celluvisc or courlose or eskalose or gelaxin or gly#ocellon or moventon or natulose or nymcel or polycel* or regucellulose or thylose or tylose or xylo mucine or xylomucin).mp. (5110)

31 (artificial* adj2 tear*).ti,ab. (960)

32 (confort or contears or optive or refresh or "tear, artificial" or unisol).ti,ab. (466)

33 pilocarpine/ (6127)

34 (pilocarpine or adsorbocarpine or akarpine or almocarpine or asthenopin or cendo carpine or chibro carpine or glucocarpine or isopto carpin* or isopto pilocarpine or isoptocarpine or isoptopilocarpine or liocarpina or milocarpine or ocu carpine or ocucarpine or ocusert or oftan or pil ofteno or pilagan or pilasite or pilo grin or pilocar or pilocarpin or pilocarpinium chloride or pilocarpol or pilofrin or pilogel or piloheptine or pilokarpin isopto or pilomann or pilomin or pilomiotin or pilopine or pilopt or piloptic or pilostat or pilosyst or pilotonina or salagen or sanpilo or sno pilo or spersacarpine or vistacarpin* or ximex opticar or zhenrui).mp. (7943)

35 (cevimeline or af 102 b or af 102b or af102b or evoxac or fsk 508 or fsk508 or saligren).mp. (192)

36 tetracycline/ (17974)

37 tetracycline*.mp. (38061)

38 or/9-37 (501984)

39 randomized controlled trial.pt. (379001)

40 controlled clinical trial.pt. (88847)

41 randomized controlled trial/ (379001)

42 random allocation.sh. (81248)

43 double blind method.sh. (126987)

44 single blind method.sh. (19364)

45 clinical trial/ (490022)

46 clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or multicenter study/ (630455)

47 (clin$ adj25 trial$).ti,ab. (272317)

48 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).ti,ab. (136078)

49 placebos.sh. (32787)

50 placebo$.ti,ab. (161336)

51 random$.ti,ab. (722809)

52 animals/ not (animals/ and humans/) (3877137)

53 or/39-51 (1425559)

54 53 not 52 (1299186)

55 8 and 38 and 54 (581)

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Database: Embase <1974 to 2014 July 18>

Search Strategy:

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1 exp *keratoconjunctivitis sicca/ (1004)

2 exp *dry eye/ (3078)

3 (dry eye adj3 (syndrome*1 or disease*1)).ti,ab. (1804)

4 keratoconjunctivitis.ti,ab. (4063)

5 xerophthalmia.ti,ab. (879)

6 sjogren$2.ti,ab. (14584)

7 (dysfunctional tear adj3 (syndrome$1 or disease$1)).ti,ab. (31)

8 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae).ti,ab. (133)

9 or/1-8 (22387)

10 *antiinflammatory agent/ (21792)

11 *cyclosporin/ (16181)

12 *cyclosporin A/ (22738)

13 (c#closporin* or cylcokat or ikervis or cipol or deximune or implanta or imusporin or vekacia or neoral or restasis or sandim* or adi 628 or adi628 or cicloral or consupren or equoral or gengraf or ol 27400 or ol27400 or pulminiq or sang 35 or sang35 or sangcya).ti,ab. (56697)

14 *corticosteroid/ (63064)

15 steroid*.ti,ab. (233692)

16 *loteprednol etabonate/ (101)

17 (loteprednol etabonate or alrex or cddd 5604 or cddd5604 or "chloromethyl 17alpha ethoxycarbonyloxy 11beta hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate" or hgp 1 or hgp1 or lotemax or loter#x or lotesoft or p 5604 or p5604).ti,ab. (133)

18 *fluorometholone/ (421)

19 (fluorometholone or "21 desoxy 6alpha methyl 9alpha fluoroprednisolone" or "21 desoxy 9alpha fluoro 6alpha methylprednisolone" or "9alpha fluoro 11beta,17alpha dihydroxy 6 alpha methylpregna 1,4 diene 3,20 dione" or cortilet or delmeson*1 or efflumidex or eflone or flosef or fluaton or flucon or fluforte liquifilm or flulon or flumelon or flumetholon* or flumex* or flumetholone or fluoph or fluro op or fluorlon or flurometholon or fluoromethalone or fluoropos or fuluson or isopto flucon or loticort or methasite or oxylone).ti,ab. (301)

20 *methylprednisolone/ (17974)

21 (methylprednisolone or "11beta,17alpha,21 trihydroxy 6 alpha methyl 1,4 pregnadiene 3,20 dione" or "6 methyl delta 1 hydrocortisone" or "6alpha methyl delta1 hydrocortisone" or adlone* or dep medalone or depmedalone or depoject or depopred or esametone or firmacort or medixon or mednin or medralone or medrate or medrol or medrone or medprednisolone or mesopren or methacort or methyl prednisolone or methylcotol* or methylpred or methylsterolone or metidrol or metrisone or metycortin or metypred or metypresol or neomedrone or nsc 19987 or nsc19987 or prednol or solomet or solu decortin or urbason).ti,ab. (17686)

22 ((occlu* or plug*) adj2 puncta*).ti,ab. (327)

23 ((lacrimal or puncta*) adj2 occlus*).ti,ab. (218)

24 *serum/ (35933)

25 *autologous serum/ (26)

26 (autologous adj2 serum*).tw. (2225)

27 *eye drops/ (3103)

28 (eye adj2 (drop*1 or instill*)).ti,ab. (5408)

29 (eyedrop*1 or opthalmic solution*1).ti,ab. (2199)

30 *acetylcysteine/ (7923)

31 (acetylcysteine or acetyl cysteine or acetyl l cysteine or acerac or acetadote or acetain or acypront or acys 5 or airbron or alveolex or bromuc or brunac or cetilan or drenaflen or ecomucyl or encore or exomuc or fabrol or flemex ac or fluim#cil or fluimukan or fluprowit or flutafin or hidonac or inspir or alpha acetamido beta mercaptopropionic acid or lappe or libramucil or "m.c.t." or menaxol or mercapturic acid or mucocil or mucofillin or mucolator or mucomiste or mucomyst or mucopect or mucoserin or mucosil or mucosof or mucosol or mucosolvin or mucosten or mucoza or mukolit or muteran or nsc111180 or nsc 111180 or parvolex or reolin or respaire or sigamucil or siran 200 or siran200 or solmucol or spatam or sputoprompt or stecin or tixair or zifluvis).ti,ab. (22445)

32 *hydroxypropylmethylcellulose/ (1736)

33 (adatocel or artelac or atract or cellugel or celulose grin or contactol or genteal or gonak or goniosoft or goniosol or hyroxypropyl methyl cellulose or hyroxypropyl methylcellulose or hydroxypropylmethyl cellulose or hypromellose or isopto* or k 8515 or k8515 or lac oph or lacrisic or lacrisifi or lubafax or methocel or methopt or methylhydroxypropyl cellulose or methylhydroxypropylcellulose or metolose or naturalag or nicotears or nova vizol or occucoat or ocucoat or opsil tears or oq coat or pharmacoat or sic opthal or tears natural ii or ultratears).ti,ab. (1075)

34 *carboxymethylcellulose/ (1978)

35 (carboxymethylcellulose or almelose or apergel or blandlax or bu lax or carbethox or carbose d or carboxy methyl cellulose or carboxymethyl cellulose or carboxy methyl cellulose or carmellose or carmethose or cel o brandt or cellofa* or cellufresh or cellulose gum or celluvisc or courlose or eskalose or gelaxin or gly#ocellon or moventon or natulose or nymcel or polycel* or regucellulose or thylose or tylose or xylo mucine or xylomucin).ti,ab. (5198)

36 *artificial tear/ (477)

37 (artificial* adj2 tear*).ti,ab. (1138)

38 (confort or contears or optive or refresh or "tear, artificial" or unisol).ti,ab. (637)

39 *pilocarpine/ (6292)

40 (pilocarpine or adsorbocarpine or akarpine or almocarpine or asthenopin or cendo carpine or chibro carpine or glucocarpine or isopto carpin* or isopto pilocarpine or isoptocarpine or isoptopilocarpine or liocarpina or milocarpine or ocu carpine or ocucarpine or ocusert or oftan or pil ofteno or pilagan or pilasite or pilo grin or pilocar or pilocarpin or pilocarpinium chloride or pilocarpol or pilofrin or pilogel or piloheptine or pilokarpin isopto or

pilomann or pilomin or pilomiotin or pilopine or pilopt or piloptic or pilostat or pilosyst or pilotonina or salagen or sanpilo or sno pilo or spersacarpine or vistacarpin* or ximex opticar or zhenrui).ti,ab. (7288)

41 *cevimeline/ (97)

42 (cevimeline or af 102 b or af 102b or af102b or evoxac or fsk 508 or fsk508 or saligren).ti,ab. (203)

43 *tetracycline/ (28785)

44 tetracycline*.ti,ab. (31396)

45 or/10-44 (514273)

46 clinical trial/ (836924)

47 randomized controlled trial/ (348387)

48 randomization/ (62711)

49 crossover procedure/ (39550)

50 double-blind procedure/ (116877)

51 single-blind procedure/ (18551)

52 placebo/ (255518)

53 random$.tw. (897968)

54 rct.tw. (14346)

55 factorial$.tw. (23553)

56 (crossover$ or cross-over$).tw. (71425)

57 placebo$.tw. (204884)

58 (double$ adj blind$).tw. (148312)

59 (singl$ adj blind$).tw. (14669)

60 assign$.tw. (242895)

61 allocat$.tw. (85212)

62 or/46-61 (1844397)

63 animal/ not (animal/ and human/) (1191855)

64 62 not 63 (1791591)

65 9 and 45 and 64 (586)

66 conference.so. (1554340)

67 conference paper/ (721422)

68 66 or 67 (2257410)

69 65 not 68 (537)

****

CENTRAL

#1 [blank line]

#2 MeSH descriptor: [Dry Eye Syndromes] explode all trees 497

#3 (dry eye near/3 (syndrome* or disease*)):ti,ab,kw 432

#4 keratoconjunctivitis:ti,ab,kw 296

#5 sjogren*:ti,ab,kw 340

#6 xerophthalmia:ti,ab,kw 100

#7 (dysfunctional tear near/3 (syndrome* or disease*)):ti,ab,kw 4

#8 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae):ti,ab,kw 20

#9 #2 or #3 or #4 or #5 or #6 or #7 or #8 1075

#10 MeSH descriptor: [Anti-Inflammatory Agents] explode all trees 11015

#11 MeSH descriptor: [Cyclosporine] explode all trees 2174

#12 (c?closporin* or cylcokat or ikervis or cipol or deximune or implanta or imusporin or vekacia or neoral or restasis or sandim* or adi 628 or adi628 or cicloral or consupren or equoral or gengraf or ol 27400 or ol27400 or pulminiq or sang 35 or sang35 or sangcya):ti,ab,kw 4988

#13 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 11333

#14 steroid*:ti,ab,kw 17301

#15 (loteprednol etabonate or alrex or cddd 5604 or cddd5604 or "chloromethyl 17alpha ethoxycarbonyloxy 11beta hydroxy 3 oxoandrosta 1,4 diene 17 carboxylate" or hgp 1 or hgp1 or lotemax or loter?x or lotesoft or p 5604 or p5604):ti,ab,kw 96

#16 MeSH descriptor: [Fluorometholone] explode all trees 57

#17 (fluorometholone or "21 desoxy 6alpha methyl 9alpha fluoroprednisolone" or "21 desoxy 9alpha fluoro 6alpha methylprednisolone" or "9alpha fluoro 11beta,17alpha dihydroxy 6 alpha methylpregna 1,4 diene 3,20 dione" or cortilet or delmeson? or efflumidex or eflone or flosef or fluaton or flucon or fluforte liquifilm or flulon or flumelon or flumetholon* or flumex* or flumetholone or fluoph or fluro op or fluorlon or flurometholon or fluoromethalone or fluoropos or fuluson or isopto flucon or loticort or methasite or oxylone):ti,ab,kw 111

#18 MeSH descriptor: [Methylprednisolone] explode all trees 1622

#19 (methylprednisolone or "11beta,17alpha,21 trihydroxy 6 alpha methyl 1,4 pregnadiene 3,20 dione" or "6 methyl delta 1 hydrocortisone" or "6alpha methyl delta1 hydrocortisone" or adlone* or dep medalone or depmedalone or depoject or depopred or esametone or firmacort or medixon or mednin or medralone or medrate or medrol or medrone or medprednisolone or mesopren or methacort or methyl prednisolone or methylcotol* or methylpred or methylsterolone or metidrol or metrisone or metycortin or metypred or metypresol or neomedrone or nsc 19987 or nsc19987 or prednol or solomet or solu decortin or urbason):ti,ab,kw 2729

#20 ((occlu* or plug*) near/2 puncta*):ti,ab,kw 54

#21 ((lacrimal or puncta*) near/2 occlus*):ti,ab,kw 73

#22 MeSH descriptor: [Serum] explode all trees 689

#23 (autologous near/2 serum*):ti,ab,kw 73

#24 MeSH descriptor: [Ophthalmic Solutions] explode all trees 2068

#25 (eye near/2 (drop* or instill*)):ti,ab,kw 1233

#26 (eyedrop* or opthalmic solution*):ti,ab,kw 537

#27 MeSH descriptor: [Acetylcysteine] explode all trees 601

#28 (acetylcysteine or acetyl cysteine or acetyl l cysteine or acerac or acetadote or acetain or acypront or acys 5 or airbron or alveolex or bromuc or brunac or cetilan or drenaflen or ecomucyl or encore or exomuc or fabrol or flemex ac or fluim?cil or fluimukan or fluprowit or flutafin or hidonac or inspir or alpha acetamido beta mercaptopropionic acid or lappe or libramucil or "m.c.t." or menaxol or mercapturic acid or mucocil or mucofillin or mucolator or mucomiste or mucomyst or mucopect or mucoserin or mucosil or mucosof or mucosol or mucosolvin or mucosten or mucoza or mukolit or muteran or nsc111180 or nsc 111180 or parvolex or reolin or respaire or sigamucil or siran 200 or siran200 or solmucol or spatam or sputoprompt or stecin or tixair or zifluvis):ti,ab,kw 1067

#29 (adatocel or artelac or atract or cellugel or celulose grin or contactol or genteal or gonak or goniosoft or goniosol or hyroxypropyl methyl cellulose or hyroxypropyl methylcellulose or hydroxypropylmethyl cellulose or hypromellose or isopto* or k 8515 or k8515 or lac oph or lacrisic or lacrisifi or lubafax or methocel or methopt or methylhydroxypropyl cellulose or methylhydroxypropylcellulose or metolose or naturalag or nicotears or nova vizol or occucoat or ocucoat or opsil tears or oq coat or pharmacoat or sic opthal or tears natural ii or ultratears):ti,ab,kw 88

#30 MeSH descriptor: [Carboxymethylcellulose Sodium] explode all trees 116

#31 (carboxymethylcellulose or almelose or apergel or blandlax or bu lax or carbethox or carbose d or carboxy methyl cellulose or carboxymethyl cellulose or carboxy methyl cellulose or carmellose or carmethose or cel o brandt or cellofa* or cellufresh or cellulose gum or celluvisc or courlose or eskalose or gelaxin or gly?ocellon or moventon or natulose or nymcel or polycel* or regucellulose or thylose or tylose or xylo mucine or xylomucin):ti,ab,kw 299

#32 (artificial* near/2 tear*):ti,ab,kw 412

#33 (confort or contears or optive or refresh or "tear, artificial" or unisol):ti,ab,kw 177

#34 MeSH descriptor: [Pilocarpine] explode all trees 250

#35 (pilocarpine or adsorbocarpine or akarpine or almocarpine or asthenopin or cendo carpine or chibro carpine or glucocarpine or isopto carpin* or isopto pilocarpine or isoptocarpine or isoptopilocarpine or liocarpina or milocarpine or ocu carpine or ocucarpine or ocusert or oftan or pil ofteno or pilagan or pilasite or pilo grin or pilocar or pilocarpin or pilocarpinium chloride or pilocarpol or pilofrin or pilogel or piloheptine or pilokarpin isopto or pilomann or pilomin or pilomiotin or pilopine or pilopt or piloptic or pilostat or pilosyst or pilotonina or salagen or sanpilo or sno pilo or spersacarpine or vistacarpin* or ximex opticar or zhenrui):ti,ab,kw 544

#36 (cevimeline or af 102 b or af 102b or af102b or evoxac or fsk 508 or fsk508 or saligren):ti,ab,kw 23

#37 MeSH descriptor: [Tetracyclines] explode all trees 1813

#38 tetracycline*:ti,ab,kw 1548

#39 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 42425

#40 #9 and #39 in Trials 512

PubMed

Search	Hits
((((((((((((dry eye disease) OR dry eye syndrome) OR keratoconjunctivitis) OR sjogren*) OR xerophthalmia) OR conjunctivitis sicca) OR keratitis sicca) OR cornea xerosis) OR xerosis conjunctivae)) AND ((((((((((((((((((("cyclosporin") OR "ciclosporin") OR steroid) OR loteprednol etabonate) OR fluorometholone) OR methylprednisolone) OR lacrimal occlusion) OR autologous serum) OR punctual occlusion) OR Ophthalmic Solutions) OR eye drop) OR eye instillation) OR eyedrop) OR acetylcysteine) OR hypromellose) OR carmellose) OR Carboxymethylcellulose Sodium) OR artificial tear) OR pilocarpine) OR cevimeline) OR tetracycline))) AND ((((((publisher[sb]) NOT pubstatusnihms) NOT pubstatuspmcsd) NOT pmcbook) OR pubstatusaheadofprint) OR in process)	96

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

The following conference proceedings were searched:

- The Association for Research in Vision and Ophthalmology annual meeting (2014)

Search term	Potentially relevant hits
Dry eye disease	17
Dry eye	96
Keratoconjunctivitis	1
Xerophthalmia	0
Sicca	5
Sjogren	2
Lacrimal	29
Ikervis	0
Cyclokat	0
Cyclosporin	1
Ciclosporin	1
Plug	6
Occlu	70
Autologous serum	1
Autologous	10
Serum	42
Tear	83
Eye drop	22
Pilocarpine	2
Cevimeline	0
Acetylcysteine	2
Mucolytic	0
Adatocel	0
Methylcellulose	1
Steroid	16
Loteprednol etabonate	1
Fluorometholone	1
Prednisolone	1
Tetracycline	2

No relevant abstracts were identified.

- The European Society of Ophthalmology annual meeting (2013)

SOE 2013 Abstract E-Book PDF (867 entries)

	Section		
Search term (control+find)	Free paper presentations (hits)	Rapid fire presentations (hits)	Electronic poster presentations (hits)
dry	6	2	15
xerophthalmia	0	0	0
keratoconjunctivitis	0	1	5
sicca	0	0	1
sjogren	1	0	1
lacrimal	1	1	13
Ikervis	0	0	0
ciclosporin	0	0	0
cyclosporin	1	2	3
cyclokat	0	0	0
plug	0	0	1
occlu	5	0	34
serum	1	1	21
autologous	0	0	9
tear	5	1	30
artificial	1	0	9
eye drop	1	1	12
pilocarpine	0	0	1
cevimeline	0	0	0
acetylcysteine	0	0	0
mucolytic	0	0	0
adatocel	0	0	0
methylcellulose	0	0	0
steroid	4	3	74
loteprednol	0	0	0
fluorometholone	0	0	0
prednisolone	0	0	13
tetracycline	0	0	0

Sections of interest (hits):

- Free Paper Presentations: Contact Lenses, Cornea, External Eye, Ocular Surface, Refractive Surgery (9)
- Rapid Fire Presentations: Cataract, Cornea, External Eye, Ocular Surface, Oculoplastics, Oncology, Pathology and Refractive Surgery (13)
- Electronic Poster Presentations: External Eye (19)
- Electronic Poster Presentations: Ocular Surface (22)

No relevant abstracts were identified.

- World Ophthalmology Congress annual meeting (2014)

Find presentations section on WOC 2014 website (2727 entries)

	Search field		
Search term	Session title (hits)	Abstract title (hits)	Abstract body (hits)
dry	45	40	21
xerophthalmia	0	0	1
keratoconjunctivitis	0	3	4
sicca	0	0	1
sjogren	0	1	1
tear	11	13	29
lacrimal	22	23	13
ikervis	0	0	0
ciclosporin	0	0	0
cyclosporin	0	0	4
cyclokat	0	0	0
plug	0	1	3
occlu	23	26	24
serum	0	4	16
autologous	0	0	1
artificial	9	7	12
eye drop	3	8	35
pilocarpine	0	0	2
cevimeline	0	0	0
acetylcysteine	0	0	0
mucolytic	0	0	0
adatocel	0	0	0
methylcellulose	0	0	0
steroid	8	13	18
loteprednol	0	0	0
fluorometholone	0	0	0
prednisolone	0	1	3
tetracycline	0	0	1

Sections of interest (topics in find presentations section) (hits):

- Anterior Segment Diseases of the Eye (12)
- External Eye Disease, Cornea, Eye Banking (164)
- Cornea, Conjunctiva (32)
- Evidence Based Ophthalmology (41)
- Ophthalmic Practice and Socioeconomics (24)
- Miscellaneous (170)
- [JOS Session] Cornea, Conjunctiva (20)
- [JOS Session] Tumor, Orbit, Eyelid, Lacrimal Functional Unit, Pathology, Pharmacology (8)
- [JOS Session] Ocular Inflammation, Infection, Uvea (10)

Poster/video section on WOC 2014 website (2134 entries)

	Search field	
Search term	Abstract title (hits)	Abstract body (hits)
dry	27	80
xerophthalmia	0	1
keratoconjunctivitis	3	14
sicca	0	5
sjogren	1	1
tear	21	115
lacrimal	14	51
ikervis	0	0
ciclosporin	0	0
cyclosporin	5	10
cyclokat	0	0
plug	0	4
occlu	47	94
serum	9	51
autologous	6	15
artificial	2	24
eye drop	9	128
pilocarpine	1	2
cevimeline	0	0
acetylcysteine	0	0
mucolytic	0	1
adatocel	0	0
methylcellulose	0	2
steroid	13	138
loteprednol	1	2
fluorometholone	0	1
prednisolone	4	30
tetracycline	0	1

Sections of interest (topics in poster/video section) (hits):

- [JOS Session] Cornea, Conjunctiva (16)
- External Eye Disease, Cornea, Eye Banking (266)
- Evidence Based Ophthalmology (7)

No relevant abstracts were identified.

Further, Santen provided three clinical study reports for Ikervis®:

- SANSIKA [NVG10E117] (phase 3: Ikervis® 1 mg/mL vs vehicle)
- SICCANOVE [NVG06C103] (phase 3: Ikervis® 0.1% vs vehicle)
- ORA [NVG08B112] (phase 2: Ikervis® 0.05% vs Ikervis® 0.1% vs vehicle)

9.2.6 The inclusion and exclusion criteria.

The following eligibility criteria were used for the systematic review:

Patients
- Adult patients (≥18 yr) with severe keratitis with dry eye disease (DED) which has not improved despite treatment with tear substitutes

Intervention
- Ciclosporin-A (Ikervis®)

Comparators
- Ciclosporin-A (CsA)
- Punctual plugs
- Permanent punctual occlusion
- Autologous serum
- Artificial tears
- Cholinergic agonists
- Acetylcysteine drops
- Topical Corticosteroids

Outcomes

Efficacy outcomes
- Corneal fluorescein staining (CFS) score assessed with the Oxford(43)/modified Oxford scale(99)7, 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)
- No restrictions on language or publication date were applied to this review
- Studies must have had a treatment or observation duration of at least 1 week
- There must been at least 20 patients included in the study analysis
- Studies including only newly diagnosed DED patients were excluded

9.2.7 The data abstraction strategy.

[7] The Oxford Scale was first proposed by AJ Bron in 1997 (The Doyne Lecture: Reflections on the tears. *Eye* (1997) 11:583-602). The Modified Oxford Scale was updated by AJ Bron in 2001 (Diagnosis of dry eye. *Surv Ophthalmol.* (2001) 45(Suppl 2): S221-226)

Customized data extraction tables were produced in Excel® and data was extracted by a single reviewer. Where data were only reported graphically these data were extracted using TechDig software. A systematic reviewer not involved in the initial data extraction process validated all data extracted against clean copies of the publications. As part of the validation process electronic PDF copies of studies were highlighted.

9.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table completed in section 6.4.

9.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See section 9.2.1

9.4.2 The date on which the search was conducted.

See section 9.2.2.

9.4.3 The date span of the search.

See section 9.2.3.

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 9.2.4.

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See section 9.2.5.

9.4.6 The inclusion and exclusion criteria.

See section 9.2.6.

9.4.7 The data abstraction strategy.

See section 9.2.7.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

See section 6.7.

9.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable.

9.6.2 The date on which the search was conducted.

Not applicable.

9.6.3 The date span of the search.

Not applicable.

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable.

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

9.6.6 The inclusion and exclusion criteria.

Not applicable.

9.6.7 The data abstraction strategy.

Not applicable.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See section 9.2.1.

9.8.2 The date on which the search was conducted.

See section 9.2.2.

9.8.3 The date span of the search.

See section 9.2.3.

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 9.2.4.

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See section 9.2.5.

9.8.6 The inclusion and exclusion criteria.

See section 9.2.6.

9.8.7 The data abstraction strategy.

See section 9.2.7.

9.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline

- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The following databases were searched:

- Medline® and Medline® In-process (OVID SP)
- Embase (OVID SP)
- EconLIT (OVID SP)
- NHS EED (CRD)

9.10.2 The date on which the search was conducted.

The search was conducted on the 15th July 2014.

9.10.3 The date span of the search.

Searches were conducted from database inception (Medline® 1946; Embase 1974; EconLIT 1898; NHS EED 1960) to 15th July 2014.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

---

1 exp Dry Eye Syndromes/ (14362)
2 (dry eye adj3 (syndrome*1 or disease*1)).ti,ab. (1491)
3 keratoconjunctivitis.ti,ab. (3657)
4 sjogren*2.ti,ab. (11898)
5 xerophthalmia.ti,ab. (766)
6 (dysfunctional tear adj3 (syndrome*1 or disease*1)).ti,ab. (27)

7 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae).ti,ab. (111)

8 or/1-7 (21284)

9 "costs and cost analysis"/ or cost-benefit analysis/ (100499)

10 quality-adjusted life years/ (7060)

11 markov chains/ (9876)

12 monte carlo method/ (20047)

13 Decision Trees/ec (1)

14 (cost$ adj3 (estimate? or variable? or effective$ or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ti. (24104)

15 (cost$ adj3 (estimate? or variable? or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ab. (34885)

16 (qoly? or hrqol or hrql or qaly? or qale? or qald?).ti,ab. (15306)

17 (economic$ or price$ or pricing or pharmacoeconomic$).ti. (40524)

18 (sensitivity adj analys#s).ti,ab. (15446)

19 (willing$ adj2 pay).ti,ab. (2959)

20 quality adjusted life.ti,ab. (6584)

21 (decision adj1 (tree$ or analy$ or model$)).ti,ab. (10408)

22 (perspective adj2 (societal or nhs or health service)).ti,ab. (2271)

23 time horizon.ti,ab. (1548)

24 budget impact analys#s.ti,ab. (176)

25 monte carlo.ti,ab. (29577)

26 markov chain.ti,ab. (3350)

27 (resource adj2 "use").ti,ab. (5156)

28 (resource adj3 (allocation$1 or utilit$)).ti,ab. (4989)

29 "cost of illness"/ (17827)

30 (economic adj3 (evaluation$ or model or analys$)).ti,ab. (12679)

31 exp models, economic/ (10236)

32 (cost or costs or costing$1).ti. (73579)

33 (cost$1 adj2 (direct or indirect)).ti,ab. (9400)

34 Health Resources/ (8901)

35 Economics, Nursing/ (3916)

36 exp Economics, Hospital/ (19576)

37 exp Economics, Pharmaceutical/ (2542)

38 exp Economics, Medical/ (13613)

39 exp "Fees and Charges"/ (27130)

40 exp Health Care Costs/ (46713)

41 burden.ti. (13554)

42 (burden adj3 (disease or illness)).ab. (13179)

43 or/9-42 (351604)

44 8 and 43 (85)

****

Database: Embase <1974 to 2014 July 14>

Search Strategy:

---

1 exp *keratoconjunctivitis sicca/ (1004)

2 exp *dry eye/ (3076)

3 (dry eye adj3 (syndrome$1 or disease$1)).ti,ab. (1803)

4 keratoconjunctivitis.ti,ab. (4061)

5 xerophthalmia.ti,ab. (878)

6 sjogren$2.ti,ab. (14571)

7 (dysfunctional tear adj3 (syndrome$1 or disease$1)).ti,ab. (31)

8 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae).ti,ab. (133)

9 or/1-8 (22371)

10 exp *economic evaluation/ (35497)

11 exp health economics/ (618957)

12 quality adjusted life year/ (12268)

13 *probability/ (3969)

14 Monte Carlo method/ (21637)

15 "decision tree"/ (5868)

16 (cost$ adj3 (estimate? or variable? or effective$ or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ti. (32534)

17 (cost$ adj3 (estimate? or variable? or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ab. (48548)

18 (qoly? or hrqol or hrql or qaly? or qale? or qald?).ti,ab. (23001)

19 (economic$ or price$ or pricing or pharmacoeconmic$).ti. (48708)

20 (sensitivity adj analys#s).ti,ab. (21756)

21 (willing$ adj2 pay).ti,ab. (4153)

22 quality adjusted life.ti,ab. (8802)

23 (decision adj1 (tree$ or analy$ or model$)).ti,ab. (13740)

24 (perspective adj2 (societal or nhs or health service)).ti,ab. (3301)

25 time horizon.ti,ab. (3049)

26 budget impact analys#s.ti,ab. (535)

27 monte carlo.ti,ab. (27450)

28 markov chain.ti,ab. (3395)

29 (economic adj3 (evaluation$ or model or analys$)).ti,ab. (16824)

30 (resource adj2 "use").ti,ab. (7125)

31 (resource adj3 (allocation$1 or utilit$)).ti,ab. (5903)

32 (cost or costs or costing$1).ti. (93973)

33 (cost$1 adj2 (direct or indirect)).ti,ab. (13951)

34 (burden adj3 (disease or illness)).ab. (17882)

35 burden.ti. (18362)

36 exp *economic aspect/ (351081)

37 or/10-36 (904262)

38 9 and 37 (224)

39 conference.so. (1545089)

40 conference paper/ (721344)

41 39 or 40 (2248081)

42 38 not 41 (179)

****

Database: Econlit <1886 to June 2014>

Search Strategy:

---

1 dry eye syndrome.mp. (0)

2 dry eye disease.mp. (0)

3 keratoconjunctivitis.mp. (0)

4 xerophthalmia.mp. (0)

5 sjogren*.mp. (5)

6 dysfunctional tear syndrome.mp. (0)

7 dysfunctional tear disease.mp. (0)

8 conjunctivitis sicca.mp. (0)

9 keratitis sicca.mp. (0)

10 cornea xerosis.mp. (0)

11 xerosis conjunctivae.mp. (0)

12 or/1-11 (5)

****

NHS EED

Line	Search for	Hits
1	MeSH DESCRIPTOR Dry Eye Syndromes EXPLODE ALL TREES	15
2	(dry eye adj3 (syndrome* or disease*))	18
3	(keratoconjunctivitis)	4
4	(sjogren*)	32
5	(xerophthalmia)	2
6	(dysfunctional tear adj3 (syndrome* or disease*))	0
7	(conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae)	0
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	55

Line	Search for	Hits
9	(#8) IN NHSEED	7

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None undertaken.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

No studies were identified.

9.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The following databases were searched:

- Medline® and Medline® In-process (OVID SP)
- Embase (OVID SP)
- EconLIT (OVID SP)
- NHS EED (CRD)

9.12.2 The date on which the search was conducted.

Searches were conducted on 15th July in EconLIT and NHS EED and on 28th July 2014 in Medline® and Embase.

9.12.3 The date span of the search.

Searches were conducted from database inception (Medline® 1946; Embase 1974; EconLIT 1898; NHS EED 1960) to 15th or 28th July 2014.

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp Dry Eye Syndromes/ (14377)
2 (dry eye adj3 (syndrome*1 or disease*1)).ti,ab. (1495)
3 keratoconjunctivitis.ti,ab. (3656)
4 sjogren*2.ti,ab. (11912)
5 xerophthalmia.ti,ab. (766)
6 (dysfunctional tear adj3 (syndrome*1 or disease*1)).ti,ab. (27)
7 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae).ti,ab. (111)
8 or/1-7 (21302)
9 *"Quality of Life"/ (53146)
10 quality of life.ti. (41164)
11 (hql or hrql or hrqol).ti,ab. (10219)
12 quality-adjusted life years/ (7094)
13 quality of life index.ti,ab. (1155)
14 cost effectiveness analys$.ti,ab. (6897)
15 economic evaluation.ti,ab. (5291)
16 Cost-Benefit Analysis/ (60570)
17 cost benefit analys$.ti,ab. (3145)
18 quality adjusted life year$.ti,ab. (6334)
19 (qaly$ or qald$ or qale$).ti,ab. (5449)
20 qwb.ti,ab. (171)
21 quality of well being.ti,ab. (333)

22 quality of wellbeing.ti,ab. (8)
23 (hui or hui 2 or hui2 or hui 3 or hui3).ti,ab. (945)
24 (time trade off or time tradeoff or tto).ti,ab. (1211)
25 (utilit$ adj2 (value$1 or cost$1 or health or analys$ or index)).ti,ab. (5836)
26 health state$1.ti,ab. (3846)
27 "Value of Life"/ (5916)
28 Health Status Indicators/ (20117)
29 daly.ti,ab. (812)
30 (hye or hyes or healthy year$1 equivalent$).ti,ab. (65)
31 standard gamble$.ti,ab. (687)
32 discrete choice experiment$.ti,ab. (493)
33 (euroqol or euroquol or EQ 5D or eq5d).ti,ab. (4346)
34 *Pain Measurement/ (9123)
35 visual analog$ scale$.ti,ab. (29729)
36 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirty-six or shortform 36 or shortform thirty six or sfthirtysix).ti,ab. (16556)
37 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or short form six or shortform six).ti,ab. (1384)
38 disutil$.ti,ab. (235)
39 willingness to pay.ti,ab. (2424)
40 (health adj3 (utilit$3 or value$2 or preference$2)).ti,ab. (7246)
41 patient preference$2.ti,ab. (4780)
42 or/9-41 (207999)
43 8 and 42 (255)
****
Database: Embase <1974 to 2014 July 25>
Search Strategy:
---
1 exp *keratoconjunctivitis sicca/ (1004)
2 exp *dry eye/ (3079)
3 (dry eye adj3 (syndrome*1 or disease*1)).ti,ab. (1805)
4 keratoconjunctivitis.ti,ab. (4064)
5 xerophthalmia.ti,ab. (880)
6 sjogren*2.ti,ab. (14595)
7 (dysfunctional tear adj3 (syndrome*1 or disease*1)).ti,ab. (31)
8 (conjunctivitis sicca or keratitis sicca or cornea xerosis or xerosis conjunctivae).ti,ab. (133)
9 or/1-8 (22401)
10 exp *"quality of life"/ (57865)
11 quality of life.ti. (56429)

12 (hql or hrql or hrqol).ti,ab. (14570)
13 quality of life index.ti,ab. (1497)
14 cost effectiveness analys$.ti,ab. (9384)
15 economic evaluation.ti,ab. (7029)
16 economic evaluation/ or "cost benefit analysis"/ or "cost effectiveness analysis"/ or "cost utility analysis"/ (163510)
17 cost benefit analys$.ti,ab. (4097)
18 quality adjusted life year$.ti,ab. (8446)
19 (qaly$ or qald$ or qale$).ti,ab. (8945)
20 qwb.ti,ab. (196)
21 quality of well being.ti,ab. (374)
22 quality of wellbeing.ti,ab. (19)
23 (hui or hui 2 or hui2 or hui 3 or hui3).ti,ab. (1306)
24 (time trade off or time tradeoff or tto).ti,ab. (1570)
25 (utilit$ adj2 (value$1 or cost$1 or health or analys$ or index)).ti,ab. (8532)
26 health state$1.ti,ab. (5701)
27 (hye or hyes or healthy year$1 equivalent$).ti,ab. (109)
28 standard gamble$.ti,ab. (792)
29 discrete choice experiment$.ti,ab. (647)
30 *pain assessment/ (6156)
31 visual analog$ scale$.ti,ab. (39818)
32 *visual analog scale/ (481)
33 (euroqol or euroquol or EQ 5D or eq5d).ti,ab. (7082)
34 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirty-six or shortform 36 or shortform thirty six or sfthirtysix).ti,ab. (23408)
35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or short form six or shortform six).ti,ab. (1509)
36 disutil$.ti,ab. (382)
37 willingness to pay.ti,ab. (3457)
38 (health adj3 (utilit$3 or value$2 or preference$2)).ti,ab. (9075)
39 patient preference$2.ti,ab. (6469)
40 or/10-39 (312861)
41 9 and 40 (272)
42 conference.so. (1558559)
43 conference paper/ (721614)
44 42 or 43 (2261821)
45 41 not 44 (222)
****

See section 9.10.4 for EconLIT and NHS EED searches.

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

9.12.6 The inclusion and exclusion criteria.

	Humanistic burden
Patients	• Adult patients (≥18 years) with severe keratitis with dry eye disease (DED) that has not improved despite treatment with tear substitutes
Intervention/ comparators	• N/A
Outcomes	• Reported utilities or scores derived using preference- based measures of health (SF-36, HUI II/III, EQ-5D, HADS, NEI-VFQ-25, OSDI, VAS)
Study design	• Primary publications only, no reviews or conference abstracts
Geographical location	• Europe, North America, Australasia
Reporting criteria	• Full publications

9.12.7 The data abstraction strategy.

See section 9.2.7.

9.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

See section 9.10.1.

9.13.2 The date on which the search was conducted.

See section 9.10.2.

9.13.3 The date span of the search.

See section 9.10.3.

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 9.10.4.

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See section 9.10.5.

9.13.6 The inclusion and exclusion criteria.

Patients	• Adult patients (≥18 years) with severe keratitis with dry eye disease (DED) that has not improved despite treatment with tear substitutes
Intervention/ comparators	• Ciclosporin-A • Punctal plugs • Permanent punctal occlusion • Autologous serum • Artificial tears • Cholinergic agonists • Acetylcysteine drops • Topical corticosteroids
Outcomes	• Direct and indirect costs • Resource use
Study design	• Primary publications only, no reviews or conference abstracts
Geographical location	• Europe, North America, Australasia
Reporting criteria	• Full publications

9.13.7 The data abstraction strategy.

See section 9.2.7.

9.14 Appendix 14: Treatment response percentages over time

Cycle	Ikervis response %	Ikervis no response %	AT response %	AT no response %	Dead
1	16.2%	83.6%	7.7%	92.1%	0.2%
2	18.7%	80.9%	7.7%	92.0%	0.4%
3	18.7%	80.7%	7.7%	91.8%	0.6%
4	18.2%	81.1%	7.5%	91.8%	0.7%
5	17.3%	81.8%	7.2%	92.0%	0.9%
6	16.3%	82.6%	6.7%	92.2%	1.1%
7	15.4%	83.3%	6.3%	92.4%	1.3%
8	14.5%	84.0%	6.0%	92.6%	1.5%
9	13.7%	84.6%	5.6%	92.7%	1.7%
10	13.0%	85.1%	5.3%	92.8%	1.9%
11	12.3%	85.6%	5.0%	92.9%	2.1%
12	11.6%	86.1%	4.7%	93.0%	2.3%
13	10.9%	86.5%	4.5%	93.0%	2.6%
14	10.3%	86.9%	4.2%	93.0%	2.8%
15	9.8%	87.2%	4.0%	93.0%	3.0%
16	9.3%	87.5%	3.8%	93.0%	3.3%
17	8.8%	87.7%	3.6%	92.9%	3.5%
18	8.3%	88.0%	3.4%	92.9%	3.7%
19	7.9%	88.1%	3.2%	92.8%	4.0%
20	7.4%	88.3%	3.1%	92.7%	4.3%
21	7.1%	88.4%	2.9%	92.5%	4.5%
22	6.7%	88.5%	2.8%	92.4%	4.8%
23	6.4%	88.6%	2.7%	92.2%	5.1%
24	6.0%	88.6%	2.6%	92.1%	5.4%
25	5.7%	88.6%	2.5%	91.9%	5.7%
26	5.4%	88.6%	2.4%	91.7%	6.0%
27	5.2%	88.5%	2.3%	91.5%	6.3%
28	4.9%	88.5%	2.2%	91.2%	6.6%
29	4.7%	88.4%	2.1%	91.0%	6.9%
30	4.5%	88.3%	2.0%	90.7%	7.2%
31	4.3%	88.2%	2.0%	90.5%	7.6%
32	4.1%	88.0%	1.9%	90.2%	7.9%
33	3.9%	87.8%	1.9%	89.9%	8.3%
34	3.7%	87.7%	1.8%	89.6%	8.6%
35	3.6%	87.5%	1.8%	89.3%	9.0%
36	3.4%	87.2%	1.7%	88.9%	9.3%
37	3.3%	87.0%	1.7%	88.6%	9.7%
38	3.2%	86.7%	1.6%	88.2%	10.1%

39	3.0%	86.4%	1.6%	87.9%	10.5%
40	2.9%	86.1%	1.6%	87.5%	10.9%
41	2.8%	85.8%	1.5%	87.1%	11.4%
42	2.7%	85.5%	1.5%	86.7%	11.8%
43	2.6%	85.2%	1.5%	86.3%	12.2%
44	2.5%	84.8%	1.5%	85.8%	12.7%
45	2.5%	84.4%	1.5%	85.4%	13.1%
46	2.4%	84.0%	1.5%	85.0%	13.6%
47	2.3%	83.6%	1.4%	84.5%	14.1%
48	2.2%	83.2%	1.4%	84.0%	14.5%
49	2.2%	82.8%	1.4%	83.6%	15.0%
50	2.1%	82.4%	1.4%	83.1%	15.5%
51	2.1%	81.9%	1.4%	82.6%	16.0%
52	2.0%	81.5%	1.4%	82.1%	16.5%
53	2.0%	81.0%	1.4%	81.6%	17.0%
54	1.9%	80.5%	1.4%	81.0%	17.6%
55	1.9%	80.0%	1.4%	80.5%	18.1%
56	1.9%	79.5%	1.4%	80.0%	18.7%
57	1.8%	78.9%	1.4%	79.4%	19.2%
58	1.8%	78.4%	1.4%	78.8%	19.8%
59	1.8%	77.9%	1.4%	78.3%	20.4%
60	1.7%	77.3%	1.4%	77.7%	21.0%
61	1.7%	76.7%	1.4%	77.0%	21.6%
62	1.7%	76.1%	1.4%	76.4%	22.2%
63	1.7%	75.5%	1.4%	75.8%	22.8%
64	1.6%	74.9%	1.4%	75.2%	23.5%
65	1.6%	74.2%	1.4%	74.5%	24.2%
66	1.6%	73.6%	1.4%	73.8%	24.8%
67	1.6%	72.9%	1.4%	73.1%	25.5%
68	1.6%	72.2%	1.4%	72.4%	26.2%
69	1.5%	71.5%	1.4%	71.7%	26.9%
70	1.5%	70.8%	1.3%	71.0%	27.7%
71	1.5%	70.1%	1.3%	70.3%	28.4%
72	1.5%	69.4%	1.3%	69.5%	29.1%
73	1.5%	68.6%	1.3%	68.8%	29.9%
74	1.5%	67.9%	1.3%	68.0%	30.7%
75	1.5%	67.1%	1.3%	67.2%	31.4%
76	1.4%	66.3%	1.3%	66.4%	32.2%
77	1.4%	65.5%	1.3%	65.6%	33.1%
78	1.4%	64.7%	1.3%	64.8%	33.9%
79	1.4%	63.9%	1.3%	64.0%	34.7%
80	1.4%	63.0%	1.3%	63.1%	35.6%
81	1.4%	62.1%	1.3%	62.2%	36.5%

82	1.4%	61.3%	1.3%	61.3%	37.4%
83	1.4%	60.4%	1.3%	60.4%	38.2%
84	1.4%	59.5%	1.3%	59.5%	39.2%
85	1.3%	58.5%	1.3%	58.6%	40.1%
86	1.3%	57.6%	1.3%	57.7%	41.1%
87	1.3%	56.7%	1.3%	56.7%	42.0%
88	1.3%	55.7%	1.3%	55.8%	43.0%
89	1.3%	54.8%	1.3%	54.8%	44.0%
90	1.3%	53.8%	1.2%	53.8%	45.0%
91	1.3%	52.8%	1.2%	52.8%	45.9%
92	1.2%	51.8%	1.2%	51.8%	46.9%
93	1.2%	50.8%	1.2%	50.8%	48.0%
94	1.2%	49.8%	1.2%	49.8%	49.0%
95	1.2%	48.8%	1.2%	48.8%	50.0%
96	1.2%	47.7%	1.2%	47.8%	51.1%
97	1.2%	46.7%	1.2%	46.7%	52.2%
98	1.1%	45.6%	1.1%	45.7%	53.2%
99	1.1%	44.6%	1.1%	44.6%	54.2%
100	1.1%	43.6%	1.1%	43.6%	55.3%
101	1.1%	42.5%	1.1%	42.5%	56.4%
102	1.1%	41.4%	1.1%	41.4%	57.5%
103	1.1%	40.4%	1.1%	40.4%	58.5%
104	1.0%	39.4%	1.0%	39.4%	59.6%
105	1.0%	38.3%	1.0%	38.3%	60.7%
106	1.0%	37.2%	1.0%	37.2%	61.8%
107	1.0%	36.2%	1.0%	36.2%	62.8%
108	1.0%	35.1%	1.0%	35.1%	63.9%
109	0.9%	34.1%	0.9%	34.1%	65.0%
110	0.9%	33.0%	0.9%	33.0%	66.1%
111	0.9%	32.0%	0.9%	32.0%	67.1%
112	0.9%	31.0%	0.9%	31.0%	68.2%
113	0.8%	29.9%	0.9%	29.9%	69.3%
114	0.8%	28.9%	0.8%	28.9%	70.3%
115	0.8%	27.9%	0.8%	27.9%	71.3%
116	0.8%	26.9%	0.8%	26.9%	72.4%
117	0.8%	25.8%	0.8%	25.8%	73.4%
118	0.7%	24.9%	0.7%	24.9%	74.4%
119	0.7%	23.9%	0.7%	23.9%	75.4%
120	0.7%	23.0%	0.7%	23.0%	76.3%

9.15 Appendix 15: QALY accumulation over time

Cycle	Ikervis cumulative QALYs	AT (no ciclosporine) cumulative QALYs
1	0.166	0.165
2	0.332	0.328
3	0.495	0.489
4	0.657	0.649
5	0.817	0.807
6	0.975	0.963
7	1.131	1.118
8	1.285	1.271
9	1.438	1.422
10	1.589	1.571
11	1.738	1.719
12	1.885	1.865
13	2.031	2.010
14	2.175	2.153
15	2.317	2.294
16	2.458	2.434
17	2.597	2.572
18	2.734	2.709
19	2.870	2.844
20	3.005	2.977
21	3.137	3.109
22	3.268	3.240
23	3.398	3.369
24	3.526	3.496
25	3.652	3.622
26	3.777	3.746
27	3.900	3.869
28	4.022	3.991
29	4.143	4.111
30	4.262	4.229
31	4.379	4.346
32	4.495	4.462
33	4.610	4.576
34	4.723	4.689
35	4.834	4.800
36	4.945	4.910
37	5.053	5.019
38	5.161	5.126
39	5.267	5.232
40	5.371	5.336

41	5.474	5.439
42	5.576	5.541
43	5.677	5.641
44	5.776	5.740
45	5.873	5.838
46	5.970	5.934
47	6.065	6.029
48	6.158	6.122
49	6.250	6.214
50	6.341	6.305
51	6.431	6.395
52	6.519	6.483
53	6.606	6.570
54	6.692	6.656
55	6.776	6.740
56	6.860	6.823
57	6.941	6.905
58	7.022	6.985
59	7.101	7.065
60	7.179	7.143
61	7.256	7.219
62	7.332	7.295
63	7.406	7.369
64	7.479	7.442
65	7.550	7.514
66	7.621	7.584
67	7.690	7.653
68	7.758	7.721
69	7.825	7.788
70	7.891	7.853
71	7.955	7.918
72	8.018	7.981
73	8.080	8.043
74	8.141	8.103
75	8.200	8.163
76	8.258	8.221
77	8.315	8.278
78	8.371	8.334
79	8.426	8.389
80	8.480	8.442
81	8.532	8.495
82	8.583	8.546
83	8.633	8.596

84	8.682	8.645
85	8.730	8.693
86	8.776	8.739
87	8.822	8.784
88	8.866	8.829
89	8.909	8.872
90	8.951	8.914
91	8.992	8.955
92	9.032	8.995
93	9.071	9.033
94	9.108	9.071
95	9.145	9.107
96	9.180	9.143
97	9.214	9.177
98	9.248	9.211
99	9.280	9.243
100	9.311	9.274
101	9.342	9.304
102	9.371	9.334
103	9.399	9.362
104	9.427	9.389
105	9.453	9.416
106	9.478	9.441
107	9.503	9.466
108	9.526	9.489
109	9.549	9.512
110	9.571	9.534
111	9.592	9.555
112	9.612	9.575
113	9.631	9.594
114	9.650	9.612
115	9.667	9.630
116	9.684	9.647
117	9.700	9.663
118	9.716	9.678
119	9.730	9.693
120	9.744	9.707

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and information submitted under ‘academic in confidence’ in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.