22 January 2015
EMA/CHMP/473489/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

IKERVIS

International non-proprietary name: ciclosporin

Procedure No. EMEA/H/C/002066

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	IKERVIS
Applicant:	Santen SAS Bâtiment Genavenir IV 1 rue Pierre Fontaine 91058 Evry Cedex FRANCE
Active substance:	ciclosporin
International Nonproprietary Name/Common Name:	ciclosporin
Pharmaco-therapeutic group (ATC Code):	Ophthalmologicals, other ophthalmologicals (S01XA18)
Therapeutic indication:	Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.
Pharmaceutical form:	Eye drops, emulsion
Strength:	1 mg/ml
Route of administration:	Ocular use
Packaging:	single-dose container (LDPE)
Package size:	30 single-dose containers and 90 single-dose containers

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List of abbreviations

ADDE	Aqueous Tear-Deficient Dry Eye
ADR	Adverse Drug Reaction
AE	Adverse Event
AN(C)OVA	Analysis Of (Co)Variance
BAK	Benzalkonium Chloride
BCRP	Breast cancer resistance protein
BFS	Blow-fill-seal
BID	Twice daily dosing
CAE	Controlled Adverse Environment Model
CEP	Certificate of Suitability of the European Pharmacopoeia
CFS	Corneal Fluorescein Staining
CHMP	Committee for Medicinal Products for Human Use
CKC	Cetalkonium Chloride
CYP	Cytochrome
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
ETDRS	Early treatment diabetic retinopathy study
EU	European Union
EQ-5D	EuroQol 5D Questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration (United States)
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HLA-DR	Human Leukocyte Antigen-DR
HPLC	High performance liquid chromatography
HPLC-MS	High-pressure liquid chromatography-mass spectrometry

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL-2	Interleukin 2
IR	Infrared spectroscopy
ITT	Intent To Treat
KCS	Keratoconjunctivitis Sicca
LC	Liquid chromatography
LDPE	Low density polyethylene
LLNA	Local Lymph Node Assay
(L)LOD	(Lower) Limit of detection
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
NOVA22007	Company code for IKERVIS formulations used in the development programme
MA(A)	Marketing Authorisation (Application)
MCT	Medium-chain triglycerides
MDR	Multidrug resistance protein
MedDRA	Medical Dictionary for Regulatory Activities
NEI-VFQ	National Eye Institute Vision Function Questionnaire
OATP	Organic anion-transporting polypeptide
OSDI	Ocular Surface Disease Index
PDCO	Paediatric Committee
PD	Pharmacodynamics
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PP(S)	Per Protocol (Set)
PT	(MedDRA) Preferred Terms
QD	Once daily dosing
RH	Relative Humidity
RMP	Risk Management Plan

TEAE	Treatment-Emergent Adverse Event
T(F)BUT	Tear (Film) Break up Time
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TLC	Thin-layer chromatography
ULOQ	Upper limit of quantification
UPLC	Ultra performance liquid chromatography
US(A)	United States (of America)
UV-Vis	Ultraviolet–visible spectroscopy
VA	Visual Acuity
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Santen SAS submitted on 2 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for IKERVIS, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 November 2011.

The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

Initially the applicant applied for the following indication: "Treatment of dry eye disease in adult patients with severe keratitis that does not improve despite treatment with tear substitutes".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ciclosporin was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0238/2012 on the granting of a product-specific waiver.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 November 2006, 24 September 2009 and 16 December 2010. The Scientific Advice pertained to insert quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturer

Manufacturer responsible for batch release

EXCELVISION
27 Rue de la Lombardière, Z.I. La Lombardière
Annonay
07100
France

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Salmon Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 2 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 31 March 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 April 2014
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 September 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 September 2014
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 November 2014.
- Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 28 November 2014
- PRAC RMP Advice and assessment overview, adopted on 4 December 2014
- During a meeting of an Expert group on 4 December 2014, experts were convened to address questions raised by the CHMP.
- Minutes of Expert group dated 4 December 2014.
- During the CHMP meeting in December 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22 January 2015, the CHMP, in the light of the overall data submitted and the

scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to IKERVIS.

2. Scientific discussion

2.1. Introduction

Problem statement

Dry eye disease (DED), also referred to as keratoconjunctivitis sicca, is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface, which is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [definition in line with 2007 International Dry Eye Workshop (DEWS)]. DED can be divided in two major classes, aqueous tear-deficient dry eye and evaporative dry eye. Aqueous tear-deficient dry eye may result from a failure of sufficient lacrimal tear secretion and can be further subdivided in Sjögren Syndrome and non-Sjögren Syndrome dry eye. Patients with Sjögren Syndrome suffer from an autoimmune disease affecting the function of lacrimal and salivary glands amongst other organs and represent a group of patients with a worse prognosis and in need of effective treatments. Evaporative dry eye is due to excessive water loss from the ocular surface caused by either intrinsic or extrinsic factors. The most common cause of evaporative dry eye disease is meibomian gland dysfunction resulting in a deficient tear film lipid layer.

Regardless of the initiating factors or groups of factors, any abnormality of the ocular surface can trigger disequilibrium in all the other components of tear dynamics. There is a common final pathway for expression of the disease, which is characterised by tear hyperosmolarity. Tear hyperosmolarity is common across all forms of DED and is central to the pathogenic mechanism of DED. It can set in motion a chain of events resulting in a vicious circle of inflammation causing further ocular surface injury. Eventually, patients can develop a self-sustaining DED with an unstable and poorly maintained tear film causing ocular signs and symptoms, which may develop into more severe forms of DED. Inflammation has a prominent role in the development and amplification of both the signs and symptoms of the disease.

The prevalence of dry eye ranges from 5%-15% in the USA, Australia, and Europe to 30-50% in Asia. Depending on the severity of the disease, patients with DED may suffer from symptoms of ocular irritation and discomfort as well as visual disturbance. Severe forms of DED are characterised by the co-existence of clinical signs including severe punctuate corneal erosion as well as constant, severe and/or disabling symptoms. However, there is usually a poor correlation between symptoms and objective clinical findings. If not effectively treated, severe disease forms may cause major ocular complications, such as infections or ulcers with potentially irreversible loss of visual acuity.

Aside from the treatment of the underlying disease or removal of external detrimental factors, if possible, the treatment of DED aims at both improving disease signs and symptoms and depends on the severity of the disease. Most patients with mild-to-moderate DED can be treated symptomatically with lubricants/artificial tears for long periods of time. Other therapeutic strategies include ocular inserts, occlusion of the lacrimal puncta, and anti-inflammatory treatment. According to DEWS, patients with moderate to severe DED are recommended to start using topical anti-inflammatory drugs such as steroids and ciclosporin. However, long-term use of corticosteroids eye drops is associated with an increased risk of side effects such as intraocular hypertension, ocular infections and cataract.

Ciclosporin formulations, from 0.05% to 2% ophthalmic emulsions in olive or castor oil, up to four times daily, have been used in clinical practice as an alternative to steroids in severe forms of DED for several decades. However, no ophthalmic ciclosporin formulation had been approved for marketing in the EU at the time of this report. In the USA, a 0.05% ciclosporin ophthalmic emulsion (Restasis®) is available to increase tear production in patients with ocular inflammation associated with keratoconjunctivitis sicca. Restasis® is available in some EU countries under compassionate use programs. In other countries, pharmacy compounded oily ciclosporin formulations are used.

About the product

IKERVIS eye drops, emulsion contains ciclosporin as active ingredient at a concentration of 1 mg/ml (0.1%) and is presented as 0.3 ml single-doses including cetalkonium chloride (CKC), a cationic surfactant to improve the residence time of ciclosporin on the ocular surface. Ciclosporin is a lipophilic cyclic polypeptide that has been used for several decades as systemic immunosuppressant for the prevention of graft rejection following organ/tissue transplantation and the treatment of various immune diseases. It has anti-inflammatory properties due to its ability to inhibit the development of cell-mediated reactions and has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2), as well as to upregulate the release of anti-inflammatory cytokines. With inflammation being a key component of the disease pathology in DED, the anti-inflammatory effect of ciclosporin is thought to be the mechanism of action in the treatment of this condition.

The applicant initially applied for the following indication:

Treatment of dry eye disease in adult patients with severe keratitis that does not improve despite treatment with tear substitutes.

The indication approved by CHMP was:

Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes (see section 5.1).

The recommended dose is one drop of IKERVIS once daily to be applied to the affected eye(s) at bedtime.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as sterile eye drops, emulsion containing 1 mg/ml of ciclosporin as active substance.

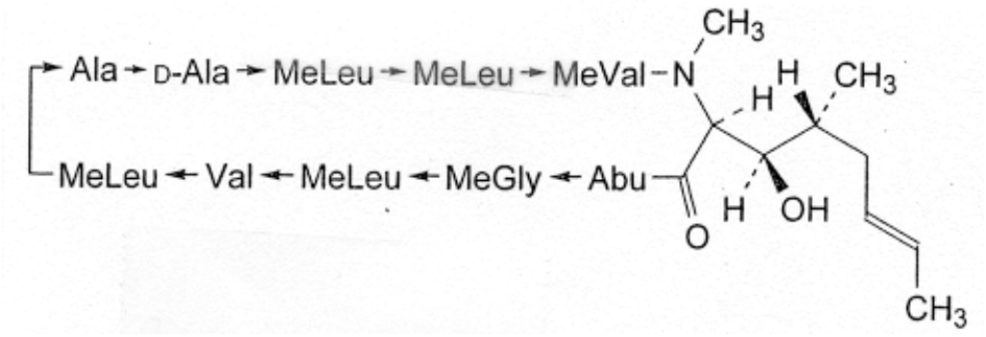
Other ingredients are: medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide and water for injections.

The product is available in 0.3 ml single-dose, low-density polyethylene (LDPE) containers presented in a sealed laminate aluminium pouch.

2.2.2. Active substance

General information

The chemical name of ciclosporin is cyclo[[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-oct-6-enoyl]-L-2-aminobutanoyl-Nmethylglycyl- N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-Nmethyl- L-leucyl-N-methyl-L-valyl] and has the following structure:



The active substance is a white to almost white powder practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

As there is a monograph of ciclosporin in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identification (IR, HPLC), appearance of solution (Ph. Eur.), specific optical rotation (Ph. Eur.), assay (Ph. Eur.), related substances (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), loss on drying (Ph. Eur.), residual solvents (GC), bacterial endotoxins and microbial testing (Ph. Eur.).

Batch analysis data on 8 batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The proposed specifications and test methods comply with the Ph. Eur. monograph and the CEP. Additional specifications have been set for residual solvents and microbial integrity (microbial enumeration tests). The GC method for determination of residual solvents is annexed to the CEP. The microbial integrity and endotoxin testing is performed according to Ph. Eur., but have been validated to demonstrate that no interferences are present.

Stability

The stability of the active substance has been evaluated by EDQM and justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a sterile, positively-charged, oil in water (o/w) emulsion that contains the active substance ciclosporin at a concentration of 1 mg/ml. The emulsion is milky-white in appearance. The finished product is packed in conventional low density polyethylene (LDPE) single dose containers containing 0.3 ml of the emulsion. The single dose containers are provided in strips of five, which are packaged in a conventional sealed laminate pouch.

The aim of the pharmaceutical development was to obtain a formulation of ciclosporin for topical ocular delivery. Due to the poor aqueous solubility of the drug the development of an emulsion was pursued. A positively charged emulsion was designed to extend the residence time on the eye (due to electrostatic attraction with the negative charge of the ocular surface) in contrast with conventional eye drop solutions, where washout of the formulation occurs rapidly after instillation. This allows once-daily dosing to be achieved.

In addition, eye drops are easy to administer and the resulting level of systemic exposure to the drug substance is reduced compared to systemic delivery.

Therefore, the development program was designed to develop an ophthalmic oil-in-water emulsion formulation that was suitable for conventional ocular instillation, easy to manufacture as a sterile product, isotonic to human tears and physically and chemically stable at room temperature.

The following key factors were considered: choice of oil solvent for drug solubilisation, choice of surfactant to stabilise the emulsion, choice of other excipients to optimise ocular tolerability, droplet size, physical and chemical stability of the formulation, impact of heat sterilisation, impact of pH drop over shelf life.

A solubility study of ciclosporin in different oily media was conducted to select the solubilising agent. The results from this study indicated that maximum solubility was achieved in medium-chain triglycerides (MCT) followed by castor oil and soybean oil. As a result, MCT, a fully saturated triglyceride was chosen. Moreover, as MCT is stable to oxidation compared to unsaturated oils, the risk of rancidity is eliminated, the use of an antioxidant is avoided and a longer shelf life can be guaranteed. MCT also has a very low viscosity, ensuring easy spreading on the eye's surface following administration.

In order to facilitate the emulsification process and to stabilise the product by decreasing the interfacial tension between oil and water the addition of a surfactant was required. Two surfactants complimentary to each other in their hydrophilic –lipophilic balance were chosen: Tyloxapol (HLB of 12.5) and Poloxamer 188 (HLB of 29) to ensure physical stability of the dispersed oil phase within the aqueous phase.

In addition, a cationic surfactant was chosen for use in the drug product based upon positive results in literature indicating that positively charged emulsions can optimise spreading and exposure of the ocular surface to the drug product. Several cationic agents were considered. During initial development benzalkonium chloride (BAK) was selected because of its extensive use in approved ophthalmic formulations, usually as a preservative. However, in this formulation it is used only as a cationic agent. This formulation was used in the initial

pharmaceutical, nonclinical and clinical development. Subsequently, the applicant decided to replace BAK with cetalkonium chloride (CKC) since this is the most lipophilic of the three homologues in BAK. The selection of CKC instead of BAK resulted in a reduction of the amount of quaternary ammonium used by a factor of 4. To determine the optimal concentration of CKC, a series of emulsions containing different concentrations of CKC were evaluated for zeta potential and droplet size distribution at the initial time point and after stress conditions (15 days at 80°C) and freeze-thaw cycles. It is acknowledged that IKERVIS emulsion does not comply with the antimicrobial effectiveness test prescribed in the European Pharmacopeia (5.1.3), which ascertains the unpreserved feature of the emulsion.

Moreover, the applicant conducted a number of studies to compare the BAK and CKC formulations to identify any potential changes in the product performance or quality specifications. The comparisons consisted of physicochemical comparison (appearance, zeta potential, droplet size, pH, osmolality, viscosity), ciclosporin assay and degradation products comparison over 36 months storage at long term conditions (25°C / 40% RH) or 6 months storage at accelerated conditions (40°C / ≤ 25% RH) and droplet size analysis. The obtained results demonstrated that the replacement of BAK by CKC does not impact the formulation.

In order to control the osmolality of the formulation, two excipients were considered sodium chloride and glycerol. The latter was chosen as sodium chloride affected emulsion stability.

Finally, sodium hydroxide was selected as ophthalmic pH adjuster, and water for injections as the aqueous diluent for the emulsion.

Well-known pharmaceutical excipients were selected to ensure good ocular tolerability of the formulation, as described above. The excipients used are compliant with Ph. Eur. standards, except CKC which is controlled through an in-house specification which includes some of the Ph. Eur. parameters applied to BAK, since CKC is a constituent of the mixture of homologues making up BAK. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of the active substance with all the excipients used in the finished product formulation has been demonstrated through development, accelerated and long term stability studies.

The drug product is a white milky emulsion intended to be applied topically to the eye and is presented in single-dose containers over-wrapped with an aluminium pouch to prevent moisture loss and protect from light.

The emulsion has been characterised in terms of type of emulsion, impact of droplet size and structure of the droplet.

Stability studies indicated that the formulation undergoes a decrease in pH over time and quickly reaches a threshold value. Since the water used in the preparation is of high quality and no ionic species are added to the formulation, a small amount of a pH decreasing substance (e.g. carbon dioxide in the atmosphere) can cause a significant fall in pH. A pharmaceutical study was conducted to evaluate the impact of the administration of an acidic drop of the drug product onto the surface of the eye. This study concluded that the pH of the tear film would remain unchanged after the administration of one drop of the proposed formulation. Therefore, the low apparent pH of the formulation is not considered as an issue regarding the quality and product attributes since no degradation of ciclosporin or physical instability have been reported along with the pH decrease over time.

The choice of the manufacturing process has been adequately justified; the critical process steps and parameters are identified. The sterility of the final product is ensured by combining a moist heat bulk sterilisation with an aseptic filling into blow-fill-seal single dose containers, since the primary packaging made of semi permeable LDPE does not allow a terminal sterilisation by heat. The method of sterilisation was selected

accordingly to the Annex to the Note for Guidance on Development Pharmaceutics detailing the Decision Trees for the selection of Sterilisation Method (CPMP/QWP/054/098 Corr).

The primary packaging is 0.3 ml single-dose, low-density polyethylene (LDPE) containers presented in a sealed laminate aluminium pouch. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: preparation of oily and aqueous phases, high shearing mixing, high pressure homogenization, sterilisation of the bulk emulsion by heat, aseptic filling utilizing the blow-fill-seal (BFS) technique and packaging.

The process is considered to be a non-standard manufacturing process since the emulsion is a specialised pharmaceutical dosage form and aseptic filling is applied. The process is generally well-described, the critical process parameters and in-process controls are specified. Process validation has been performed on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise: appearance, identification (HPLC, HPLC/UV, TLC), pH (Ph. Eur.), osmolality (Ph. Eur.), zeta potential (electrophoretic mobility), mean droplets size (dynamic light scattering), uniformity of dosage units (content uniformity) (Ph. Eur.), assay (Ph. Eur.), related substances (Ph. Eur.), sterility (Ph. Eur.).

The proposed specifications are in line with ICHQ6A and general Ph. Eur. requirements and are acceptable. However, there is scope for further tightening of the pH limits. Due to the limited batch analysis data at the time of opinion, the applicant is recommended to re-evaluate the pH specification limit in light of new stability data from the next 10 new commercial scale batches.

Beside compendial methods, in-house analytical methods are used for identification and assay of the active substance, determination of degradation products by HPLC/UV as well as for zeta potential and mean droplets size. The in-house methods have been adequately validated.

Batch analysis results are provided for 3 pilot scale and 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three pilot scale batches and three full scale batches stored under long term conditions (25 ºC / 40% RH) and under intermediate conditions (30 ºC / 65% RH) for up to 36 months (pilot batches), and up to 6 months (full scale batches), as well as under accelerated conditions (40°C/≤25%RH) for 6 months according to the ICH guidelines were provided. The batches of IKERVIS are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, osmolality, zeta potential, mean droplet size, assay, related substances and sterility.

The applicant performed forced degradation studies as a part of the validation of the HPLC method for related substances. The studies confirmed that isociclosporin A is the main degradation product under acidic, oxidative, heat and light conditions. It can also be concluded that the analytical method is stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

A freeze-thaw cycle testing (24-hour freezing cycle at -18 °C, followed by thawing for 4 hours at 60°C) and shipment stability testing (at 50°C during 2 weeks, 5°C during 2 and 4 weeks and -20°C during 2 weeks (with one freeze-thaw cycling after 1 week) was performed. The results from these studies confirm that the product the product quality is not affected by temperature excursions that might occur during transportation.

The product was stable over the time-period studies. All results remained well within the proposed shelf life specifications and no trend was noted in any of the parameters tested apart from a drop of pH during photo-stability testing. This led to the conclusion that the product has to be protected from light as described in the SmPC.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A positively charged oil-in-water emulsion has been designed to extend the residence time of ciclosporin on the eye allowing a once-daily dosing. The choice of excipients used in the formulation has been well justified and it has been demonstrated by a number of studies that a physically and chemically stable emulsion with good ocular tolerability was produced. The manufacturing process has been well described and adequately validated. The results of tests carried out indicated consistency and uniformity of important product quality characteristics, and these in turn led to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

The applicant is recommended to re-evaluate the pH specification limit post-approval, based on new stability data from the next 10 new commercial scale batches.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development programme for IKERVIS was abridged and focused on the investigation of the disposition of ciclosporin after single and repeated administrations, in order to quantify the local and systemic exposure following ocular administration, and the examination of the topical effects in toxicology testing. Given that ciclosporin is a known active substance that has been used for several decades in the prophylaxis of organ rejection following transplantation as well as in the treatment of immune and inflammatory disorders, the pharmacodynamic effect is well described in the scientific literature and therefore, no non-clinical pharmacology studies have been conducted by the applicant. Furthermore, as the systemic exposure after ocular instillation of IKERVIS was negligible, no genotoxicity, carcinogenicity or reproductive and developmental toxicity studies were performed. Instead, the applicant made reference to published studies in the scientific literature concerning administration of ciclosporin via other routes.

Some of the non-clinical studies were performed with a former formulation containing benzalkonium chloride (BAK) at a concentration of 0.02% w/w, which was replaced in the final formulation proposed for approval by cetalkonium chloride (CKC) at a concentration of 0.005% w/w. This was considered in principle acceptable in a previous scientific advice provided by the CHMP in 2010, given that BAK is a mixture of quaternary ammonium compounds including CKC and at a concentration of 0.02% w/w contains more CKC than the final IKERVIS formulation, thus representing a worst case scenario in the safety assessment (see section 2.3.3. for a comparison of the PK profiles of both formulations).

2.3.2. Pharmacology

The mechanism of action of ciclosporin is well known and has been described in numerous publications in the scientific literature (see section 2.4.3). Animal models exactly reflecting the human pathology of DED were not available at the time of this report and therefore no non-clinical pharmacology studies have been conducted by the applicant.

The use of ocularly administered ciclosporin has also been documented in the treatment of DED/KCS. DED is a multifactorial condition in which increased osmolarity of the tear film, T-cell mediated inflammation and cytokine production, decreased production of mucins and goblet cell death are observed. Beneficial effects of topical ocular ciclosporin for the treatment of tear deficiency in DED were first reported over 20 years ago in dogs with KCS showing that topical ciclosporin has a marked lacrimogenic effect (Kaswan et al., 1989, Olivero et al., 1991, Kaswan et al., 1994, and Gao et al., 1998). Further data showed that ciclosporin exerts its therapeutic effect on KCS not only by inhibiting T-cells and increasing goblet cells, but also by increasing Aquaporin 3 expression in the conjunctiva (Sun et al., 2005), and through an antagonist effect on prolactin. The inhibition of apoptosis appears also to be a key mechanism for the therapeutic effect of ciclosporin for KCS (Strong et al., 2005).

According to ICH S7A guideline 'safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low'. As these conditions were met for IKERVIS (see section 2.3.3. and 2.4.2. for systemic absorption of ciclosporin after ocular administration), no safety pharmacology studies were conducted.

Ciclosporin is known to interfere with efflux transporters, by being both at substrate and an expression modulator of P-glycoprotein (P-gp/MDR1) (Bohme et al., 1994) and by inhibiting MRP1 (Bobrowska-Hagerstrand et al, 2007). Multidrug resistance protein 1 (MDR1), multidrug resistance-associated proteins 1–6 (MRP1–6) and breast cancer resistance protein (BCRP) were found in ocular tissues (Karla et al., 2009). Prostaglandin analogues and their free acid forms are substrates of MRP1, MRP2, and MRP5 (Hariharan et al., 2009), and thus it might be possible that ciclosporin modulates the ocular transport of these molecules. Since MRP1 is mainly localised in the basal cells of the corneal epithelium, its inhibition may results in a lower absorption of the prostaglandin analogues into the anterior chamber (aqueous humor). However, the clinical significance of efflux transporters modulation is still not clearly determined for antiglaucoma therapies.

2.3.3. Pharmacokinetics

The goal of the pharmacokinetic (PK) nonclinical programme was to characterise the ocular biodisposition of ciclosporin following single and multiple ocular administrations of IKERVIS (NOVA22007), and to compare it with Restasis (0.05%), which is authorised in the USA for the treatment of KCS and was used as a reference product because it was the only other ciclosporin-containing eye drop formulation available for human use at the time of this report. To this end, the applicant performed single and multiple dose studies in rabbits. Validated HPLC-MS, UPLC-MS/MS and LC-MS/MS methods were used for the determination of ciclosporin concentrations in rabbit whole blood and various ocular tissues (cornea, conjunctiva). The limits of quantification ranged from 0.1 ng/ml in whole blood to 50 ng/g in the cornea.

Absorption

The formulation used for the non-clinical PK studies included BAK (0.02% w/w), which was later replaced by CKC (0.005% w/w) in the final formulation applied for. Furthermore, the old formulation included vitamin E, which was no longer present in the new formulation. In order to confirm that the ocular PK profile of the two formulations was comparable, the applicant performed a single dose study in rabbits. The study showed that the exchange of BAK for CKC and removal of vitamin E had no effect on the overall ocular PK parameters in the conjunctiva and cornea. Both maximum concentrations (c_{max}) and areas under the curve (AUCs) measured for the two formulations in ocular tissues were comparable.

- Ocular tissue

NOVA22007 concentrations increased dose proportionally in the cornea and conjunctiva after both single and multiple instillation of 50 µl of NOVA22007 0.25, 0.5 and 1 mg/ml and displayed half-lives of 3.19-6.68 hrs and 26.21-53.25 hrs in conjunctiva and cornea, respectively. Maximum concentration (cmax) was attained generally at 0.33 hrs. No (conjunctiva) or slight (cornea) accumulation of ciclosporin in ocular tissues was observed following multiple administrations. The AUC levels of ciclosporin in the cornea were found to be doubled after a single instillation of NOVA22007 (0.5 mg/ml) compared to single installation of Restasis 0.5 mg/ml. Conjunctival AUC levels were similar for both formulations. Following repeated administrations (for ten days) of NOVA22007 0.1% QD tissue ciclosporin concentrations (Cmin) were observed in the cornea at steady state similar to those observed following a 10-day treatment with Restasis (0.05%) BID.

- Systemic exposure

Whole blood ciclosporin exposure as measured in rabbits following single or multiple instillations of 50 µl of NOVA22007 up to a strength of 1 mg/ml was shown to be negligible with all values < LOD (limit of detection) of 0.1 ng/ml.

Distribution and metabolism

Radioactivity levels were measured in ocular (including cornea and conjuctiva) and non-ocular tissues of rabbits treated with ^{3}H-ciclosporin formulations for 7 days, at 1 hour and 24 hours after the last administration. The highest radioactivity levels were found in external ocular structures, and low levels were observed in deep ocular tissues. Some levels of radioactivity were found in systemic organs which the applicant considered to be likely due to the presence of radiolabelled ciclosporin metabolites considering that the higher count levels were found in the major elimination organs, liver and kidney.

No additional drug metabolism or drug interaction studies have been performed by the applicant as ophthalmic ciclosporin metabolism could not be demonstrated in dogs and rabbits (Acheampong 1999, Wiederholt 1986).

2.3.4. Toxicology

Single and repeat dose toxicity

The applicant did not perform any single dose toxicity studies due to the low systemic exposure after ocular use of IKERVIS. However, four repeat-dose toxicity studies were performed with NOVA22007 in rabbits to investigate local tolerance (see below).

Genotoxicity, carcinogenicity and reproduction toxicity

As the systemic exposure after ocular instillation of IKERVIS was negligible, the applicant did not perform genotoxicity, carcinogenicity or reproductive and developmental toxicity studies, and instead summarised relevant information from the scientific literature. Ciclosporin is referred to in the literature as a non-genotoxic human carcinogen (McClain 2001, Hernandez 2009). The carcinogenic potential has been reported previously (Ryffel 1992, Durnian 2007), however excessive immunosuppression allowing for uncontrolled cellular growth was not expected at the doses used with an ocular topical application of ciclosporin 1 mg/ml, even in eye tissues.

There are no adequate and well-controlled studies in pregnant or breast-feeding women with either oral ciclosporin or other ciclosporin ophthalmic dosage forms, however Ryffel (1983) reported no teratogenic effects for ciclosporin when investigated in different animal species, but there is some evidence for reproductive toxicity at high (maternal toxic) doses.

Local tolerance

Local tolerance of NOVA22007 was investigated in four repeat-dose toxicity studies in rabbits with instillations in the eyes four times a day for 28 days to investigate local tolerance (see below). Two of these studies used a ciclosporin formulation with BAK and two used the CKC formulation. Additionally, corneal sensitivity following repeated instillation of NOVA22007 was examined in a study with rabbits.

NOVA22007 was well tolerated at concentrations of 0.25, 0.5 and 1 mg/ml instilled at 4-hour and 90 minute intervals. Slight signs of irritation mainly in nictitans membrane and eyelids were noted in all treated animals, as well as in animals administered the vehicle alone. Slight conjunctival redness was observed for NOVA22007 1 mg/ml but no histopathological findings were reported. Moreover, slight transient conjunctiva irritation reactions accompanied with focal unilateral and chronic conjunctivitis on the bulbar conjunctiva were also noted in a study with NOVA22007 containing 0.005% w/w CKC. These findings were also seen in an untreated eye and were considered attributable to the daily repeated instillations. Minor epithelial ulcerations or linear marks of the cornea seen in the same study were considered attributable to slight traumatisms and not treatment related.

Removal of Vitamin E and the change of the excipient from 0.02% w/w BAK to 0.005% w/w CKC had no impact on the ocular tolerance of the formulation.

NOVA22007 1 mg/ml and its vehicle did not cause any anaesthesia of the cornea in rabbits.

Other toxicity studies

The applicant furthermore performed a Local Lymph Node Assay (LLNA) assay in mice to evaluate the skin sensitisation potential of the vehicle of NOVA22007 as well as a murine UV-LLNA assay and a study in guinea pigs to assess the phototoxic and photoallergic potential. Finally, the applicant presented the results of three non-GLP studies examining different safety attributes of the cationic emulsion in rabbits.

The LLNA assay showed that neither the BAK nor CKC containing formulations induced delayed contact hypersensitivity. NOVA22007 was devoid of phototoxic and photoallergic potentials in the guinea pig. Finally, the results of the murine UV-LLNA assay demonstrated that the product was devoid of phototoxic and photoallergic potential.

In the first of the three studies investigating the safety of the cationic emulsion (Liang 2008), both BAK and CKC containing cationic emulsions proved safer and well tolerated by ocular surface tissue when compared to their equivalent aqueous solutions. The second study (Liang 2012b) demonstrated that NOVA22007 0.5 mg/ml containing 0.005% CKC was again well tolerated and was comparable to other BAK/CKC free ciclosporin formulations (i.e. Restasis and ciclosporin oil solution) as assessed by both Draize test and in vivo confocal microscopy irritation scores. Finally, to assess the effects of the cationic emulsion/formulations on corneal wound healing, the applicant examined the effects of the cationic emulsion containing 0.005% w/w CKC onto damaged cornea (Liang 2012a). Results indicated that the cationic emulsion was well tolerated by altered corneal epithelium and had a positive effect on cell survival and migration compared to 0.02% w/w BAK aqueous solution.

2.3.5. Ecotoxicity/environmental risk assessment

The predicted environmental concentration in the surface water (PECsurfacewater) of ciclosporin was calculated to be 0.00025 µg/L, which is below the action limit of 0.01 µg/L. F_{pen} was set at the default value of 1%, as the overall market penetration segment was estimated at 0.30% based on published epidemiology data.
Furthermore, ciclosporin is not a PBT (persistent, bioaccumulative and toxic) substance as log Kow does not exceed 4.5. Therefore, the CHMP concluded that IKERVIS was not expected to pose a risk to the environment.

Table 1 – Summary of main study results

Substance: ciclosporin			
CAS-number: 59865-13-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	El Tayar et al., J Med Chem, 1993	2.92	Potential PBT (N)

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.92	not B
	BCF	n/a	n/a
Persistence	DT50 or ready biodegradability	n/a	n/a
Toxicity	NOEC or CMR	n/a	n/a
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater	0.00025	µg/L	< 0.01 threshold (N)
Other concerns (e.g. chemical class)	n/a	n/a	(N)

2.3.6. Discussion on non-clinical aspects

Pharmacodynamics

Animal models exactly reflecting the human pathology of DED were not available at the time of this report. Therefore and since the pharmacodynamic effect of ciclosporin is well described in the scientific literature, the CHMP considered the absence of primary pharmacodynamic studies acceptable.

The lack of secondary pharmacodynamic and specific safety pharmacology studies was also considered acceptable by the CHMP in view of the negligible systemic passage of ciclosporin after ocular treatment with IKERVIS (see also PK discussion). The CHMP considered that the maximum dose of ciclosporin administered to patients treated with IKERVIS in line with the dose recommendations of 1 drop daily was very low compared to the doses used in patients treated with ciclosporin in other indications, e.g. when compared to systemic doses of ciclosporin used to prevent graft rejections, there was a >2000 safety margin.

The clinical relevance of ciclosporin's possible interference with efflux transporters within the eye was not entirely clear at the time of this report (see PK discussion below). To avoid absorption interference and partial wash out of the product due to the excess instilled volume, the SmPC recommends that IKERVIS should be instilled at bedtime and should not be administered concomitantly with other eye drops, which was considered adequate by the CHMP.

Pharmacokinetics

The exchange of BAK for CKC and removal of vitamin E in the final IKERVIS formulation was shown not to have an effect on the overall ocular PK parameters measured in the conjunctiva and cornea, which was considered reassuring by the CHMP considering that several non-clinical studies had been conducted with the old BAK (and vitamin E) containing formulation only.

No (conjunctiva) or slight (cornea) accumulation of ciclosporin in ocular tissues of rabbits was observed following multiple administrations, reflecting the highly vascularised conjunctiva environment where clearance is significantly greater compared to the cornea.

Systemic exposure after ocular administration of IKERVIS up to a strength of 1 mg/ml was found to be negligible. However, in an ocular autoradiographic study in rabbits, some levels of radioactivity were found in systemic organs, which was attributed by the applicant to the presence of radiolabelled ciclosporin metabolites. The CHMP considered this explanation difficult to interpret given that data in the scientific literature suggest that ciclosporin is not metabolised in the eye (at least in animals, see discussion below). However, as ciclosporin is a well-known active substance, the significance of this finding was considered limited.

No additional drug metabolism studies have been performed by the applicant considering that ophthalmic ciclosporin metabolism has not been demonstrated in dogs and rabbits (Acheampong 1999, Wiederholt 1986). However, the CHMP considered that the available literature data were controversial. The results of a publication in patients suggest that ciclosporin is extensively metabolised in the human eye (Althaus et al., 1996). So far, these data have not been corroborated by animal data and cytochrome CYP450 expression profiles in human corneal epithelium, and alternative explanations for the results of Althaus et al. such as an increased vascular permeability and reduce retinal barrier in the investigated patient population have been proposed. It is known that numerous phase I and phase II metabolic enzymes are present in the human eye, including cytochrome (CYP) enzymes, but data in the scientific literature (Kolln, 2012) suggest that these enzymes have minor or non-existent roles in the fate of drugs in the cornea. Therefore, the CHMP agreed that further drug metabolism studies were not warranted.

The CHMP, having considered the totality of the data including the scientific literature, furthermore accepted that no in-vitro or in-vivo drug interaction studies were carried out with IKERVIS. While, ciclosporin is known to be a strong inhibitor of several transporters such as P-gp (MDR1), BCRP, MRP and OATPB1 (organic anion-transporting polypeptide B1), only transporters of the MRP family and BCRP are expressed and functional in human cornea. The applicant acknowledged that inhibition of MRPs in theory might lead to a decreased passage through the cornea of prostaglandin analogues used in the treatment of glaucoma, a condition which might co-exist in DED patients. The risk was considered by the applicant to be low, as either the inhibitory effect of ciclosporin on the efflux proteins normally expressed in the cornea (MRP 1, BCRP) was rather weak, or the level of expression of the proteins in the eye was low (MRP2, MRP4). There was no evidence in the scientific literature regarding interaction of ciclosporin with MRP4 or MRP5. Furthermore, while, compared to Restasis (0.05%), which was the only other approved (though only in the USA) ciclosporin-containing eye drop formulation at the time of this report, corneal ciclosporin concentrations will be higher immediately after instillation of IKERVIS 0.1%, similar exposure rates would be expected for both formulations at steady-state because IKERVIS is given once a day and Restasis is used twice a day. Thus, no increased risk for interactions deferred from increased local exposure, would be expected.

The applicant proposed to further explore possible drug-drug interactions in a study, which would aim at obtaining information at the transporter level (two year study program), as well as at the cellular level (one year study program). The study proposal was welcomed by the CHMP and considered useful to further explore the interaction potential of ciclosporin. The CHMP recommended that the study be conducted post-authorisation.

Finally, the CHMP noted that IKERVIS contains poloxamer 188. Poloxamers are known to interact with transporters like BCRP (Giri et al, 2009) and MRPs (Shaik et al, 2008). Still, the interaction potential was considered small because of the high water solubility of poloxamer 188 and since the water phase of the tear film is eliminated from the pre-corneal space within few minutes after instillation. Hence, the concentration of Poloxamer 188 on the ocular surface decreases rapidly and the remaining impact of the expected low concentration on the transmembrane efflux proteins was presumed to be minor.

Toxicology

Systemic exposure to ciclosporin after ocular use was found to be negligible and thus the risk of systemic side effects due to circulating ciclosporin levels was considered to be low, justifying the lack of certain toxicological tests, including any genotoxicity, carcinogenicity or reproductive and developmental toxicity studies. However, since ciclosporin has been shown to have a carcinogenic potential, peri-ocular skin cancer, conjunctival or corneal neoplasia was included in the risk management plan (RMP) as an important potential risk. This was agreed by the CHMP although the risk was considered low at the doses used with the ocular topical application of IKERVIS.

No overt adverse effects attributable to IKERVIS were identified in the local tolerance toxicity studies. The CHMP considered that the conduct of these studies was in line with the Note for Guidance on non-clinical local tolerance testing on medicinal products (CPMP/SWP/2145/00). Although DED is a chronic disease requiring long-term use of IKERVIS, the application period for local tolerance testing should generally not exceed four weeks, and therefore 28 days was considered by the CHMP to be an acceptable observation time using the same dose as proposed for clinical use.

The use of the BAK formulation in some of the studies was considered acceptable in line with a previous scientific advice by the CHMP in 2010, given that BAK is a mixture of quaternary ammonium compounds including CKC and, at a concentration of 0.02% w/w contains more CKC than the final IKERVIS CKC formulation proposed for approval. Thus, the BAK formulation may be considered a worst case scenario in the safety assessment. CKC is furthermore well-known and, at the time of this report, was already used in marketed products and medical devices within the EU. Results from studies in mice furthermore indicated that the cationic emulsions were generally well tolerated and a positive effect on cell survival and migration was seen for the CKC formulation compared to BAK aqueous solution. As these studies were not conducted in line with GLP, the evidence was only considered supportive. However, this data in addition to the known safety profile of CKC in marketed products and the local tolerance studies performed with NOVA22007 1 mg/ml containing CKC was considered by the CHMP sufficient to support the use of CKC in the final product from a toxicology perspective.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data were considered by the CHMP sufficient to support the application for a marketing authorisation for IKERVIS in the treatment of severe keratitis in adult patients with dry eye that does not improve despite treatment with tear substitutes. The CHMP furthermore concluded that IKERVIS was not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

Good Clinical Practice (GCP)

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study name (Number)	No of randomised patients	Dose of NOVA22007 Comparator Duration of treatment	Primary objective
Phase II studies providing design information for Phase III			
Phase IIa (N09F0502)	53 Sjögren patients with moderate to severe DED	NOVA22007 (0.025%; 0.05% or 0.1%) Vehicle One drop BID	Safety and tolerability as primary objective
Phase IIb ORA (NVG08B112)	132 Patients with mild to moderate DED	NOVA22007 (0.05% or 0.1%) Vehicle One drop QD 3 months	Dose finding, to test the hypothesis that NOVA2207 is superior to its vehicle, using a CAE
Phase III study providing design information for the pivotal Phase III			
Phase III SICCANOVE (NVG06C103)	495 Patients with moderate to severe DED	NOVA22007 0.1% Vehicle One drop QD 6 months	To compare NOVA22007 to its vehicle
Phase III pivotal study			
Phase III SANSIKA (NVG10E117)	246 Patients with severe DED	Part 1: NOVA22007 0.1% or Vehicle One drop QD 6 months Part 2: 6 month open label extension	To compare the efficacy of NOVA 22007 to its vehicle and assess long-term safety of NOVA22007 over a 12 month period
On going study			
Phase III Post-SANSIKA (NVG10E117)	67 Patients with severe DED	NOVA22007 0.1% One drop QD 24 months	To assess the duration of the improvement following NOVA22007 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 $\geq$ 4 to CFS $\leq$ 2.

2.4.2. Pharmacokinetics

As IKERVIS is intended for topical use, no specific PK studies were performed. However, in order to evaluate a possible systemic exposure to ciclosporin as a result of the ocular administration of IKERVIS, blood samples were collected in patients included in the Phase IIa study and in the 2 Phase III clinical studies (SANSIKA and SICCANOVE) and ciclosporinemia was measured using a specific validated HPLC-MS/MS assay (LLOQ of 0.1 ng/mL and LLOD of 0.05 ng/mL). The other method used in the Phase IIa safety study was an HPLC-MS assay with a LLOQ of 2 ng/ml.

In study N09F0502 (see section 2.5.1. for a brief description), performed in 2006 in 53 patients with Sjögren syndrome, detectable ciclosporin blood levels were reported in only 2 patients treated with NOVA22007 0.05% following one month and three months of treatment respectively. In one patient, a ciclosporin blood level of 23.9 ng/mL was found at one month of treatment and in the other patient a ciclosporin blood level of 19.9 ng/ml was found at three months of treatment. These results were considered by the applicant to be likely due to a

cross-contamination of the blood samples during their handling, as the values are substantially higher that what would be expected assuming complete absorption of the instilled eye drops.

In the SICCANOVE study (described in more detail in section 2.5.2.3.), 184 patients (85 who received IKERVIS and 99 vehicle) were assayed for ciclosporinaemia at baseline (Day 0) and after 6-month treatment (Day 168). Most of the patients (170/186) were below LLOD after 6-month treatment. Amongst the 322 samples analysed, 16 showed detectable ciclosporin levels with 12 samples being below LLOQ, and 4 with a quantifiable level (0.102, 0.110, 0.123 and 0.155 ng/ml).

In the SANSIKA study (described in more detail in section 2.5.2.) ciclosporin blood levels were measured at baseline, and at Months 6 and 12. At baseline 5/213 patients had quantifiable levels as they were already receiving systemic ciclosporin, which was allowed during the study as per the study protocol, provided treatment remained stable throughout the course of the study. At Month 6, 187 patients were assayed and most of them had negligible systemic exposure to ciclosporin: 157 were below LLOD, 23 were below LLOQ, 7 had measurable ciclosporin levels including 3 patients with measurements beyond the ULOQ of 5 ng/mL as they were receiving systemic ciclosporin. The other values ranged from 0.126 to 0.206 ng/mL At Month 12, the systemic exposure profile appeared consistent with the profile observed until Month 6 (56 patients with <LLOD values, and 19 patients with <LLOQ values), whether the patient received IKERVIS for 12 months or whether the patient was switched to IKERVIS after 6 months on placebo. Measurable samples were detected in 7 patients and ranged from 0.105 to 1.27 ng/mL at end of study (Month 12). Two patients had values beyond the ULOQ due to use of systemic ciclosporin.

2.4.3. Pharmacodynamics

No specific pharmacology studies were conducted with IKERVIS since an adequate model of DED does not exist and since ciclosporin is a well-known active substance for which the mechanism of the immunosuppressive and anti-inflammatory actions has already been well-described in the scientific literature.

Ciclosporin acts via passive entry into cells, reversible binding to cyclophilin A causing inactivation of calcium-dependent activation of the cell. The resultant immunosuppressive effect is caused by the inhibition of IL-2 production (as well as of other cytokines), inhibition of clonal expansion of T lymphocytes including mainly helper CD4 cell and its subsets (Noble, 1995, Donnenfeld 2009) and is reversible when treatment is stopped.

Over recent years, inflammation of the ocular surface has been shown to be key in the pathogenesis of DED. Tear hyperosmolarity leads to irritation of the surface of the eye and promotes inflammation, involving cytokine secretion by epithelial cells as well as activation of the T-cells lymphocytes. An increase in soluble and cellular inflammatory mediators in the tear fluid (IL-1, IL-8, TNF-α, and MMP-9), conjunctiva and lacrimal glands has been reported (Furuichi et al, 2002; Li et al., 1981; Luo Let al., 2003; Rosette et al., 1996), which initiates an inflammatory cascade on the ocular surface, evidenced by increased expression of immune activation and adhesion molecules (HLA-DR and ICAM-1) by the conjunctival epithelium. Increased HLA-DR antigen expression by the conjunctival epithelium detected by flow cytometry has been observed as a universal feature of dry eye (Baudouin et al., 2000). Secretion of pro-inflammatory cytokines sustains and intensifies the inflammatory response (Meggs 1993; Mircheff et al 1998; Gao et al 1998), causing further ocular surface injury. The inflammatory response has been shown to consist of inflammatory cell infiltration, epithelial activation, increased concentrations of cytokines and other inflammatory factors, and increased activity of matrix-degrading enzymes (Baudouin et al 1997; Tishler et al 1998; Afonso et al 1999; Pflugfelder 1999; Pflugfelder 2000; Sobrin et al 2000). This key role of inflammation in the pathogenic mechanism of DED is the basis for the anti-inflammatory treatment approach.

2.4.4. Discussion on clinical pharmacology

As there is no adequate model of DED and since IKERVIS is used locally and there was no evidence of significant systemic absorption, the CHMP considered it acceptable that no specific clinical pharmacology studies were conducted. Ciclosporin is a known immunosuppressant and anti-inflammatory agent and the mechanism of action has been well documented in the scientific literature. As inflammation has been shown to be key to the pathology of DED and has been postulated to be part of a vicious circle leading to a self-sustained disease state, the CHMP considered it plausible that anti-inflammatory therapies could be effective in the treatment of DED.

While it is possible that systemic absorption of ciclosporin could occur through the nasal mucosa as a result of the eye drops being cleared from the ocular surface through the lachrymal draining system, PK samples collected in the phase IIa and the two phase III trials with IKERVIS, suggested that absorption of and resulting systemic exposure to ciclosporin after ocular instillation of IKERVIS was negligible.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the view that the available information in the scientific literature as well the PK data collected in the clinical trials were sufficient to support the application for IKERVIS in the treatment of severe keratitis in adult patients with DED from a clinical pharmacology perspective. Given the local route of administration and that no significant systemic exposure was observed, the CHMP considered that the lack of specific pharmacodynamics or pharmacokinetic studies was acceptable.

2.5. Clinical efficacy

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

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

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

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

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

Use from 8 December 2009 (EMEA/622721/2009) to minimise the concentration of the quaternary ammonium compounds and related toxicity. One study in each Phase (II and III) was conducted with the BAK formulation and the CKC formulation. The formulation proposed for registration contains CKC and was used in the pivotal Phase III SANSIKA study.

2.5.1. Dose response studies

The selection of the dose used in SANSIKA, i.e. one drop of NOVA22007 0.1% (1mg/ml) once daily at bedtime, was based on the results of the pharmacokinetic studies conducted in rabbits as well as available data from the IKERVIS clinical trials programme.

Based on the studies in rabbits, described in more detail in section 2.3.3. of this report, the applicant concluded that NOVA22007 0.1% QD appeared to be similar to Restasis BID (approved for treatment of DED in the US) in terms of target tissue exposure (cornea and conjunctiva) in rabbits.

Selection of the dosing regimen was further supported by the results of the 2 Phase II clinical studies and by the Phase III SICCANOVE supportive study:

Phase IIa study N09F0502

Study N09F0502 was a multicentre, double-masked, randomised, parallel group, vehicle-controlled pilot study to assess the use of 3 different concentrations of NOVA22007 (0.025%, 0.05% and 0.1%, one drop BID) administered twice daily in Sjögren patients with moderate to severe DED after 12 weeks of treatment. The study recruited 53 patients with 46 patients completing the study. The main objective was to assess ocular tolerance and safety as well as systemic safety. Efficacy was also assessed as a secondary objective although the study was not powered to show a difference between treatment groups.

In addition to the confirmation of the Sjögren status, the main inclusion criteria were corneal fluorescein staining (CFS) scored ≥2 on the modified Oxford scale, at least 3 symptoms (i.e., burning/stinging, foreign body sensation, itching, eye dryness, pain, blurred vision or sticky feeling or photophobia) scored >1 on a 4-point scale, and corneal staining scored ≥4 on the van Bijsterveld scale.

CFS, Schirmer test, Lissamine Green, and Tear Film Break-up Time (TBUT) were used to assess effects on signs of DED. Symptoms unrelated to study drug instillation or HLA-DR expression were used to support the assessment of safety /tolerability. DED symptoms were furthermore assessed using the Global Related Subjective Ocular Symptom Score.

The percentage of improved patients for CFS in the worst eye was similar in all treatment groups (including vehicle), ranging from 70-82%. An improvement in CFS in the worst eye occurred in the four treatment groups from Day 7 and was maximal at the end of the study. Similar improvements in all four treatment groups were also observed for the Schirmer test and Tear Film Break-up Time (TBUT) and a slightly more pronounced global trend towards improvement in the mean Lissamine Green total score in the worst eye was observed for NOVA22007 0.025% and 0.1%. The mean symptom score was higher in the three active treatment arms compared to vehicle. The applicant concluded that, as compared to the 2 other concentrations (0.025% and 0.05%, one drop BID), IKERVIS 0.1% showed the most consistent improvement in both ocular symptoms and objective signs (improvement of corneal staining after 3 months of treatment).

Phase IIb study NVG08B112 (ORA)

ORA (NVG08B112) was a multicentre, double-masked, randomised, vehicle-controlled dose finding study conducted in the US in patients with mild to moderate DED for a duration of 3 months. The study used a Controlled Adverse Environment (CAE), a clinical model that provides a standardised approach to studying investigational treatments of dry eye by exacerbating the signs and symptoms of dry eye (e.g. corneal staining and ocular discomfort) in a controlled manner by regulating humidity, temperature, airflow, lighting conditions and visual tasking within the CAE chamber.

Patients were randomised into the study on a 1:1:1 basis to receive one drop QD of either IKERVIS, 0.05%, IKERVIS 0.1% or vehicle. A total of 132 patients were randomised and 120 completed the study (42, 36 and 42 in the IKERVIS 0.05%, IKERVIS 0.01% and vehicle groups, respectively). The main inclusion criteria were a corneal staining scored ≥2 on the ORA scale, a Schirmer test without anesthesia scored ≥ 1 and ≤ 10 mm, a response when exposed to the CAE as evidenced by a) an ocular discomfort scored ≥ 3 for two consecutive measurements within the CAE in at least 1 eye and b) a ≥1 increase in CFS in the inferior region as measured by the ORA scale post-CAE in at least one eye. The ORA scale is a 5-point scale to evaluate symptoms/ocular discomfort. ORA score was the average of all time points during CAE exposure (graded by the subjects every 5 minutes during the 90 minutes exposure). At baseline all patients were scored 3 in average.

The study failed to meet its objective on the co-primary endpoints, which were combining mean CFS and mean ocular discomfort based on the ORA scale after 3 months. The analysis of the secondary endpoint of CFS improvement showed a statistical significant effect in favour of the 0.05% group (reduction of CFS of 0.3 units compared to vehicle), but not for the 0.1% group. This result was considered by the applicant to be explained by the small sample size which was based on an over-expectation of the magnitude of the treatment effect at the planning stage of the study (expected effect size = 0.75), thus suggesting that the absence of a significant effect for the higher dose could be a chance finding. For the ocular discomfort endpoint, the test result indicated no significant treatment group difference, with patients' symptoms being similarly and largely improved in all 3 treatment groups. Furthermore, for both investigated NOVA22007 concentrations improvement trends in several dry eye sign and symptom secondary endpoints compared to baseline were observed.

Phase III SICCANOVE study

The SICCANOVE study is described in more detail in section 2.5.2.3. A statistically significant improvements of CFS (component of the co-primary endpoint) and of the percentage of CFS responders (post-hoc analsysis) were observed for NOVA22007 0.1% QD compared to vehicle.

Conclusion

With regards to safety, the applicant argued that the selected dose of one drop NOVA22007 0.1% QD has been shown to be safe in clinical studies and there was no significant systemic exposure to ciclosporin neither in non-clinical studies (see section 2.3.3.) nor in the Phase IIa and phase III clinical studies (see section 2.4.2.).

Therefore, mainly based on the PK results observed in rabbits as well as in the phase IIa study and in the absence of safety concerns in any of the tested doses, the highest strength of 0.1% was retained for the pivotal Phase III trial SANSIKA and is also proposed for the commercial formulation.

2.5.2. Main study(ies)

SANSIKA (study NVG10E117): A multicentre, randomised, 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 CYCLOKAT® 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe dry eye disease (DED)

Methods

Study Participants

Centres from 9 countries recruited patients for this study: 22 sites in France, 11 sites in Germany, 12 sites in Italy, 14 sites in Spain, 3 sites in Belgium, 1 site in the UK, 1 site in Sweden, 2 sites in Austria, and 1 site in Czech Republic.

SANSIKA enrolled patients presenting with persistent severe DED for which artificial tears was the usual background treatment. Only adult patients were recruited, which is in line with the proposed target population and the fact that DED rarely occurs in children. In line with inclusion/selection criteria, patients were to be symptomatic and had a severe and well defined keratitis, a corneal lesion known to cause visual morbidity.

Inclusion Criteria

- Male or female aged 18 years and over.
- Persistent **severe DED** at the Screening and Baseline Visits defined as follows:
    - Corneal Fluorescence Staining (CFS) score of 4 on the modified Oxford scale, AND
    - Schirmer test without anaesthesia scored ≥2 mm/5 min and <10 mm/5 min, AND
    - Ocular Surface Disease Index (OSDI) score ≥23.

Exclusion criteria

Ocular Conditions/Diseases

- CFS grade of 5 or below 4 on the modified Oxford scale.
- DED resulting from the destruction of conjunctival goblet cells or scarring.
- Any relevant ocular anomaly other than DED interfering with the ocular surface including trauma, post radiation keratitis, Stevens-Johnson syndrome, corneal ulcer history, etc.
- Abnormal lid anatomy, abnormalities of the nasolachrymal drainage system or blinking function in either eye.
- 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.
- Active herpes keratitis or history of ocular herpes.
- History of ocular trauma or ocular infection (viral, bacterial, fungal, protozoal) within 90 days before the Screening Visit.

- History of non-infectious ocular inflammation not associated with dry eye (e.g. uveitis, scleritis, peripheral ulcerative keratitis).
- 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.
- 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.
- Active rosacea and/or progressive pterygium.
- History of ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis other than dry eye.
- Use of contact lenses during the study.
- 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:
    - Ocular laser/surgery other than 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.
    - 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

- Use of topical ciclosporin (e.g. Restasis), tacrolimus or sirolimus within 90 days before the Screening Visit. These treatments were also prohibited during the course of the study.
- Use of topical corticosteroids, antibiotics, pilocarpine, antihistamines, or BAK preserved IOP lowering medications within 30 days before the Screening Visit. These treatments were also prohibited during the course of the study.
- Use of any artificial tears other than those provided by the study sponsor during the course of the study.

Systemic Conditions/Diseases or Treatments

- 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., oestrogen-progesterone or other oestrogen derivatives [only for post-menopausal women], pilocarpine, isotretinoin, 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.
- Disease not stabilised within 30 days before the Screening Visit (e.g., diabetes with glycaemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections) or judged by the Investigator to be incompatible with the study.
- Presence or history of severe systemic allergy.

- Any change in systemic immunosuppressant drugs within 30 days before the Screening Visit or anticipated change during the course of the study.
- Known hypersensitivity to 1 of the components of the study or procedural medications (e.g., fluorescein, lissamine green, etc.).
- History of malignancy in the last 5 years.
- Pregnancy or lactation at the Baseline Visit.
- 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 vasectomised 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

- History of drug addiction or alcohol abuse.
- 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.
- Participation in a clinical trial with an investigational substance within the past 30 days.
- Participation in another clinical study at the same time as the present study.

Treatments

During the 6 month double masked period, referred to as 'Part 1', patients were to be enrolled and randomised to receive one drop of either NOVA22007 0.1% (IKERVIS) or vehicle (negative control) once daily (QD) in each eye at bedtime.

The subsequent 6 month open label extension follow-up period, referred to as 'Part 2', was designed to generate safety data over the whole duration of the 12-month study. During Part 2, all patients were to receive NOVA22007.

Patients who completed the 12 month study attended a total of 7 visits:

- 5 visits during Part 1: Screening Visit (Day -14 to -7), Baseline Visit (Day 0), Month 1 Visit (Day 28±3 days), Month 3 Visit (Day 84±7 days) and Month 6 Visit (Day 168 ±14 days);
- 2 visits during Part 2: Month 9 Visit (Day 252±14 days) and Month 12 Visit (Day 336±14 days).

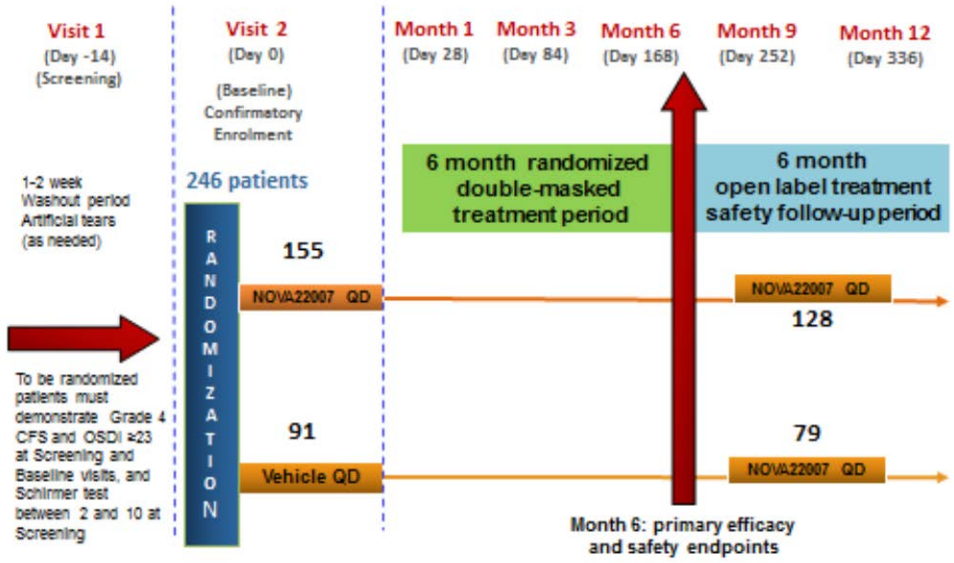


Figure 1 – Design of the phase III SANSIKA trial

Investigational Drug

NOVA22007 is a sterile, ophthalmic cationic oil-in-water emulsion containing 0.1% ciclosporin.

Vehicle Control

Vehicle was a sterile, drug-free, cationic ophthalmic oil-in-water emulsion. The formulation was identical to NOVA22007 but without ciclosporin (NOVA22007 0%).

Concomitant Artificial Tears

Patients were allowed to use unpreserved artificial tears (only those provided by the sponsor) as often as needed. Patients were instructed not to use artificial tears within 30 minutes before or after use of the study medication. Patients were also instructed not to use the artificial tears 2 hour before the study visit.

Objectives

Primary Objective

The primary objective of this study was to demonstrate the superiority of 1 mg/mL ciclosporin eye drop emulsion (NOVA22007) over vehicle administered once daily in simultaneously improving signs and symptoms in patients with severe DED after 6 months of treatment.

Secondary Objective

The secondary objective was to evaluate the ocular tolerability and overall ocular safety of NOVA22007 administered once daily in patients with severe DED at 2 time points:

- at Month 6, after the randomised, double-masked treatment period, and

- at Month 12, after the open label follow-up period.

Outcomes / endpoints

Efficacy was to be only determined in the "analysis eye", which was defined as the worst eligible eye, i.e. the eligible eye with the higher lissamine green staining score at baseline. If both eyes were eligible and had the same lissamine green staining score at baseline, the eye with the worst Schirmer test score at baseline was used. If both eyes had the same Schirmer test score at baseline, the right eye was used.

Primary efficacy endpoint

The primary endpoint was 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 based on the modified Oxford scale (i.e. change in CFS ≤-2), and
- improvement by 30% or more from Baseline in OSDI (i.e. % change ≤-30%).

Secondary efficacy endpoint

- CFS responders at Month 6: patients with a 2 grade or more improvement in CFS score assessed based on the modified Oxford scale.
- OSDI responders at Month 6: patients having an improvement in OSDI score of at least 30%.
- Composite responder at Month 6: patients with a 2 grade or more improvement of CFS score assessed with the modified Oxford scale AND an improvement in the Visual Analogue Scale (VAS) of Ocular Discomfort score of at least 30%.
- VAS responder at Month 6: patients having an improvement in the VAS score of at least 30%.

Other secondary efficacy endpoints

- CFS score assessed with the Modified Oxford Scale at Months 1, 3 and 6.
- OSDI score at Months 1, 3, and 6.
- VAS score at Months 1, 3 and 6.
- Schirmer Test score without anaesthesia at Month 6.
- Complete Corneal Clearing at Month 6.
- Artificial Tear use at Months 1, 3 and 6.
- Investigator Global Evaluation of Efficacy at Month 6.

Other outcomes

- Impression Cytology for Conjunctival Cell Surface Human Leukocyte Antigen-DR (HLA-DR) Expression at Months 1 and 6.
- Tear Break Up Time (TBUT) at Month 6.
- Lissamine Green Staining score at Months 1, 3 and 6.
- Quality of Life Questionnaires (NEI-VFQ/EQ-5D) at Month 6.
- Tear Film Osmolarity at Months 1 and 6.

Furthermore, post hoc analyses were performed

- with the primary endpoint setting the threshold of improvement of CFS at 3 grades;

- with the CFS responder rate, setting the threshold of improvement of CFS at 3 grades;

- with the primary efficacy endpoint at Months 1, 3 and 6;

- with tear film osmolarity in patients with a score higher than 308 mOsms/L at baseline.

Efficacy variables

– Corneal Staining

In general, punctate staining of the cornea is not normal and the presence of punctuate staining suggests the loss of epithelial cell membrane or junctional integrity. The modified Oxford grading system and the van Bijsterveld scale are widely used and standardised methods to estimate ocular surface damage. More specifically, the modified Oxford grading system, a 7-point ordinal scale (0, 0.5, and 1 to 5), was used to evaluate corneal fluorescein staining (CFS) in all phase III and phase II studies. In this system a grade 0 represents complete corneal clearing (absence of staining dots). With the van Bijsterveld scale, staining is graded 0 to 3 on the cornea and for two exposed conjunctival areas (range: 0–9).

– Symptom scores

The Ocular Surface Disease Index (OSDI) was designed to assess symptoms of ocular irritation and their impact on vision-related functions. It also allows the grading of dry eye severity. All 12 questions of the OSDI are scored from 0 (none) to 4 (all the time) although seven questions could be answered as “not applicable”.

In addition to OSDI, each symptom was assessed using a Visual Analogue Scale (VAS) of Ocular Discomfort, VAS (0-100), as a secondary endpoint. 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. Symptoms were assessed in each eye and the data was used to calculate the global VAS assessment for both eyes.

– Use of artificial tears (AT)

Most of the patients were already receiving AT prior to enrolment into the study. During the wash-out period and throughout the studies, patients were allowed to use unpreserved ATs as frequently as needed. The number of estimated unpreserved AT provided by the sponsor was calculated as the difference in weight of unused and used AT bottles during the period, assuming that 1g of artificial tears contains 33.3 drops.

– Schirmer test

The Schirmer test without anaesthesia is a well-standardised test performed with the patient’s eyes closed. There is wide intra-subject, temporal, and visit-to-visit variation, with the variation and the absolute decrease in aqueous deficiency being mostly due to the decreased reflex response with lacrimal failure. A low score on a Schirmer test is an indication for aqueous deficiency. The lower the score, the lower the tear production, whereby a score of 10 or more suggests normal aqueous tear production. Patients with severe to moderate aqueous deficiency would typically score in the range of 0 to 5. The diagnostic cut off frequently used at the time of this report was <5.0 mm in 5 minutes.

– HLA-DR expression

Flow cytometry is a minimally invasive objective metrics and was used to determine HLA-DR levels on conjunctival epithelial cell surfaces. HLA-DR is an immune-related marker normally expressed by immune-competent cells, and has been shown to be up-regulated in epithelial cells in cases of autoimmune and inflammatory disorders, and inflammation in the ocular surface. In DED, conjunctival and lacrimal acinar cells have been shown to over-express this marker at very high levels, especially, but not only, in patients with Sjögren's syndrome. Flow cytometry was therefore used to determine inflammatory levels in patients with DED and monitoring topical ciclosporin effects. HLA-DR expressions was quantified in Arbitrary Units of Fluorescence [AUF] and in percentages of conjunctival cells expressing HLA-DR (HLA-DR+).

– Tear osmolarity

Tear hyperosmolarity, which is common across all forms of DED, is considered to be a global marker of DED (Lemp et al, 2011), and shown to correlate with disease severity. Osmolarity values above 308mOsm/L appear to be indicative of DED (Foulks et al, 2009; Lemp et al, 2011). Osmolarity was measured using the TearLab Osmolarity System with minimal disturbance of the tear film. For this parameter, the worst eye at each visit was used as this was considered more meaningful than analysing the same eye throughout the study. The post-hoc analysis was conducted on a subset of patients who had elevated tear film osmolarity at baseline (>308 mOsms/L).

– Tear film breakup time (TFBUT)

Tear film breakup time (TFBUT) is generally regarded as a test for diagnosis of evaporative dry eye. However, there is now good evidence that TFBUT alone is not a good differentiator for evaporative dry eye (Arita et al, 2010). With traditional volumes of fluorescein (5 µl as used as per the protocol), TFBUTs in normal subjects is >10 seconds versus ≤10 seconds in those with dry eyes (Tomlinson et al, 2011).

– Health Related Quality of Life (HRQL)

In the absence of a valid and specific instrument to measure impact of DED on patient's health status at the time SANSIKA was started, two instruments were used: the NEI-VFQ, an ophthalmic specific questionnaire, and the EQ-5D, a generic health questionnaire.

The National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) is a 25-item questionnaire, which was developed to comprehensively assess the influence of visual impairment on the multiple dimensions of HRQL, including emotional and well-being aspects, and visual functioning. A score of 100 indicates the best possible score, and 0 indicates the worst score. A 5-point difference on the NEI-VFQ-25 has been shown to be a minimal criterion for a visual impairment-related difference. Of specific interest in the study of dry eye is the ocular subscale score composed of 2 questions with a focus on ocular pain.

The EQ-5D is a simple indirect utility and generic questionnaire designed to measure health outcome. It is applicable to a wide range of health conditions and treatments and as such has limited disease-specific sensitivity and is lacking discriminative properties. It consists of five attributes, with three levels per attribute. The dimensions of the EQ-5D include: Mobility, Self- Care, Usual Activities, Pain/Discomfort, and Anxiety/ Depression. In addition to these five dimensions, a visual analogue scale (VAS) for Overall QoL is included. A total score for the five domains is calculated. In addition, the VAS is scored as a separate measure. A total score of 1.00 indicates 'full health'.

Sample size

Based on the data of the Phase III study SICCANOVE in moderate to severe DED patients, a sample size of approximately 225 evaluable patients (150 in the active group and 75 in the vehicle group, according to a 2:1 ratio) was calculated to provide at least 90% power to detect a difference between NOVA22007 and vehicle in the main analysis at Month 6. In order to take into account a potential small percentage of patients (10%) not evaluable for efficacy, a total number of at least 252 patients was calculated to be required for this study (168 in the active group and 84 in the vehicle group).

Randomisation

Each patient who provided written informed consent, and who complied with the inclusion and exclusion criteria at both the Screening Visit and Baseline Visit (Day 0) was randomly assigned to one of the two treatment groups (NOVA22007 0.1% or vehicle) using a 2:1 allocation ratio. A computerised randomisation scheme was used. Randomisation was centralised using an interactive voice response system and an interactive web response system and was stratified by centre.

Blinding (masking)

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. Each patient received a treatment unit number by the study site.

During the first 6 months of the study (Part 1), the study medication (NOVA22007 or vehicle) was double-masked. In the second 6 months of the 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, centre staff, and patients had to remain masked to the prior randomised treatment assignments until all patients had completed the 12 month study.

Statistical methods

The Full Analysis Set (FAS) was used as the primary population for the efficacy analysis. The FAS comprised all patients randomised into the study that received any amount of the study drug and were analysed according to randomised treatment (intention-to-treat principle).

The Safety Analysis Set (SAF) was used for reporting safety data; this included all randomised patients for whom there was any evidence that they used study medication and for whom any follow-up data were available. Safety analyses were performed using the actual treatment received.

The Per-Protocol (PP) population excluded patients in the FAS with any major protocol deviations that could impact the efficacy analysis.

During part 2, efficacy analyses were descriptive and conducted in the FAS-OPEN. Responder endpoints (CFS-OSDI, CFS, OSDI, global VAS and CFS-VAS responder rates, complete corneal clearing rate) were analysed using frequency distributions and exact 95% confidence intervals (95% CI). Other efficacy endpoints were analysed using means or medians (and standard deviations or range).

A summary of the statistical methods applied to the primary and secondary endpoints as well as for the post-hoc analyses for part 1 of the study is provided below. Statistical testing was conducted at a two-tailed significance level of 0.05 for all tests, except for the test on the “treatment by pooled country” interaction effect on the primary efficacy variable (significance level of 0.10). No adjustments were made for multiplicity because the

primary test of the primary endpoint was performed only once and the other efficacy results were considered supportive. Statistical testing was only performed for data of the analysis eye.

Primary endpoint

The primary composite responder endpoint was analysed at Month 6 on the FAS using imputed data. A logistic regression model, referred to as the main logistic model, was carried out with 2 factors, "treatment" and "pooled country". Sensitivity analyses were also performed, using the main logistic model on the Per Protocol Set (PPS), on the FAS using observed data, on the FAS considering the actual treatment received, and use of a Cochran-Mantel-Haenszel test controlling for pooled country.

Secondary and other efficacy endpoints

Secondary and other efficacy endpoints were analysed on the FAS and the PPS. CFS, OSDI, VAS and CFS-VAS responder rates, and complete corneal clearing rate were analysed using the main logistic model using imputed data.

Analyses of CFS, OSDI, global VAS, and lissamine green total score change from baseline at each time point (Months 1, 3, and 6) were performed using a repeated measures analysis of variance (ANOVA) with the following fixed factors: "treatment", "visit", "pooled country", and "treatment by visit" interaction. The same model was used to estimate the treatment effect at Month 6, and if significant, the treatment effect at Month 3, and if significant, the treatment effect at Month 1.

Schirmer test, TBUT, NEI-VFQ-25 and EQ-5D scales, impression cytology (after a logarithmic transformation for HLA-DR [AUF]) and tear film osmolarity were analysed using an analysis of covariance (ANCOVA) model with the following fixed factors: "treatment" and "pooled country", and the baseline score as covariate. The Shapiro-Wilk test was used to evaluate the normality of the residuals. A supportive analysis was conducted using a Cochran-Mantel-Haenszel test controlling for pooled country.

The investigator global evaluation of efficacy was analysed using a Cochran-Mantel-Haenszel test controlling for pooled country.

Descriptive statistics were used to analyse the use of artificial tears.

Post hoc analyses

The post hoc analyses for the primary efficacy endpoint (composite CFS-OSDI responder rate) as well as the secondary endpoint of CFS responder rate setting the threshold of improvement of CFS at 3 grades instead of 2 was conducted on imputed data and observed data, using the main logistic model. The primary efficacy variable at Months 1, 3 and 6 was furthermore analysed through a generalised mixed model. The post-hoc analysis of tear film osmolarity was conducted on the change from baseline at Month 6 using an ANCOVA model and taking the worst value of osmolarity between the 2 eyes (eligible or not) at each visit.

Handling of missing values

For the primary endpoint as well as the secondary responder/non-responder endpoints (CFS, OSDI, VAS, CFS-VAS responder rates and complete corneal clearing rate), missing data were imputed as follows:

- 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 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.

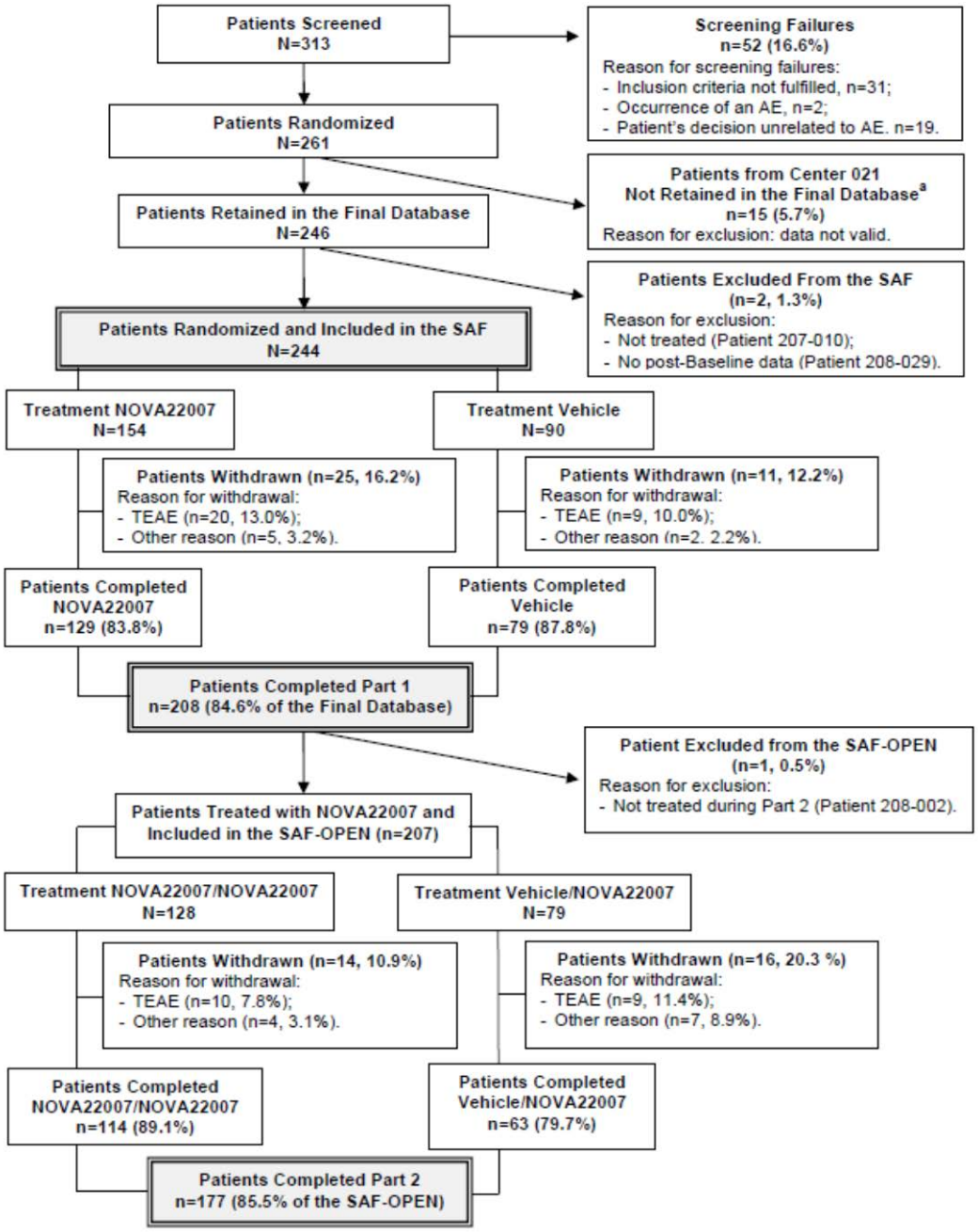
If the evaluation was missing and the patient did not discontinue before the Month 6 Visit:

- a 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.

Furthermore, for the primary endpoint a secondary analysis was performed on observed data.

Results

SANSIKA - Participant flow



Recruitment

A total of 313 patients were screened and 261 were randomised to two treatment groups in a 2:1 ratio (155 to NOVA22007 and 91 to Vehicle). A total of 52 patients failed screening prior to randomisation. The main reasons for screening failures were patients failing to meet the protocol inclusion criteria. Patients from one study centre (n=15, 5.7%) were omitted from in the analysis, due to an inspection outcome revealing breaches with GCP which led to concerns on the reliability of the data. As a result, 246 randomised patients were retained in the final database.

The study initiation date was 31 March 2011 (first patient first visit). The completion date of part 1 was 2 July 2012 (last patient Month 6) and of part 2 it was 13 February 2013 (last patient Month 12).

Conduct of the study

There were no amendments to the study protocol. However, there were a number of modifications to the planned statistical analyses, as detailed in the statistical analysis plan which was finalised prior to database lock.

Baseline data

In the FAS, the overall mean age was 61.3 years (range 22.9 to 87.6 years), with 85.3% of the patients being females of which 73.2% were post-menopausal. A total of 37.6% of the patients had Sjögren's syndrome. Almost all patients had a diagnosis of severe DED in both eyes (239/245, 97.6%). The overall mean time since diagnosis was 9.1 years (range: 0.2 to 31.5 years), and all patients were having artificial tears at study entry (10 drops/day in average).

Table 2 – Demographic Characteristics

	NOVA22007 N=154	Vehicle N=91	Total N=245
Age (years)	N=154	N=91	N=245
Mean (SD)	60.80 (13.47)	62.14 (11.76)	61.30 (12.85)
Median	61.74	63.46	62.52
Range (min;max)	(22.9-87.6)	(32.7-86.3	(22.9-87.6)
Gender	N=154	N=91	N=245
Female, n (%)	126 (81.8)	83 (91.2)	209 (85.3)
Male, n (%)	28 (18.2)	8 (8.8)	36 (14.7)
Sjögren's syndrome (n;%)	N=154	N=91	N=245
Number of patients (%)	58 (37.7)	34 (37.4)	92 (37.6)
Time since diagnosis (years)	N=153	N=91	N=244
Mean (SD)	8.80 (7.09)	9.71 (6.71)	9.14 (6.95)
Median	6.24	8.67	6.80
Range (min;max)	(0.2;31.5)	(0.2;30.7)	(0.2;31.5)

The proportion of patients presenting any eye disorder other than DED was similar in both treatment groups (40.3% in the NOVA22007 group and 35.2% in the control groups). Diseases/medical procedures were reported in a higher proportion of patients in the NOVA22007 group than in the vehicle group for cardiac disorders (14.3% vs. 7.7%), immune system disorders (11.7% vs. 5.5%), and surgical and medical procedures (12.3% vs. 3.3%) respectively. In contrast, respiratory, thoracic and mediastinal disorders were reported in a higher proportion of patients of the vehicle group (14.3%) than in the active group (7.1%). There were no other differences between treatment groups. There were no marked differences between treatment groups regarding the proportion of patients reporting the use of concomitant medications. Some patients also received systemic corticosteroids, immunosuppressants including systemic ciclosporin (n=5), or beta-blockers.

Numbers analysed

Of the 246 patients enrolled, only one patient (not treated) had no baseline data and was excluded from the FAS (245 patients). One more patient (not treated) was excluded from the Safety Analysis Set (SAF), which thus included 244 patients.

A total of 42 patients from the FAS had at least 1 major protocol deviation in part 1; 27 (17.5%) in the NOVA22007 group and 15 (16.5%) in the vehicle group. All 42 FAS patients having major protocol deviations were excluded from the PPS.

Outcomes and estimation

Primary endpoint: CFS-OSDI responder rate

Based on imputed data (according to randomised 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%). The difference in favour of NOVA22007 (5.5%) was not statistically significant.

When considering imputed data according to the actual treatment received or observed data (i.e. not imputing missing data), the difference in favour of the NOVA22007 group increased further but remained not statistically significant.

Table 3 – CFS-OSDI response at Month 6 (FAS)

	NOVA22007	Vehicle	p-value[b]
Imputed data (according to the randomized treatment group)			
N	154	91	
Responders, n (%)[a]	44 (28.6)	21 (23.1)	p=0.326
Non-responders, n (%)	110 (71.4)	70 (76.9)	
Imputed data (according to the actual treatment received)			
N	155	90	
Responders, n (%)[a]	45 (29.0)	20 (22.2)	p=0.208
Non-responders, n (%)	110 (71.0)	70 (77.8)	
Observed data			
N[c]	131	82	
Responders, n (%)[a]	43 (32.8)	20 (24.4)	p=0.152
Non-responders, n (%)	88 (67.2)	62 (75.6)	

CFS: corneal fluorescein staining; OSDI: ocular surface disease index questionnaire; n: number of patients.
[a] 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%).
[b] p-value for treatment effect in the logistic regression model.
[c] Total sample size for this analysis was 213 (131+82 patients), i.e. there were 32 missing data.

Similar results were found in the PP population. Based on imputed data, there was no statistically significant difference in the CFS-OSDI responder rate between treatment groups (36 patients, 28.3%, with NOVA22007, versus 17 patients, 22.4%, with vehicle) and between pooled countries.

Secondary endpoints: Responder/Non-Responders including complete corneal clearing

There were no statistically significant differences in CFS responder rate, OSDI responder rate, VAS responder rate and CFS-VAS responder rate between NOVA22007 and vehicle. The responder rate at Month 6 tended to be higher for CFS, assessing corneal surface integrity (51.9% with NOVA22007, 45.1% with vehicle), compared to the variables assessing symptoms of ocular discomfort (OSDI: 39.6% with NOVA22007 versus 39.6% with vehicle; VAS: 31.2% with NOVA22007 versus 37.4% with vehicle).

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 significant.

Similar results were found in the PP population.

Table 4 - CFS, OSDI, VAS and CFS-VAS Response and Complete Corneal Clearing at Month 6 (FAS)

	NOVA22007 N=154	Vehicle N=91	p-value[f]
CFS response[a]			
Responders, n (%)	80 (51.9)	41 (45.1)	p=0.346
Non-responders, n (%)	74 (48.1)	50 (54.9)	
OSDI response[b]			
Responders, n (%)	61 (39.6)	36 (39.6)	p=0.939
Non-responders, n (%)	93 (60.4	55 (60.4)	
VAS response[c]			
Responders, n (%)	48 (31.2)	34 (37.4)	p=0.302
Non-responders, n (%)	106 (68.8)	57 (62.6)	
CFS-VAS response[d]			
Responders, n (%)	35 (22.7)	19 (20.9)	p=0.744
Non-responders, n (%)	119 (77.3)	72 (79.1)	
Complete Corneal Clearing[e]			
Yes, n (%)	10 (6.5)	4 (4.4)	p=0.428
No, n (%)	144 (93.5)	87 (95.6)	

Data provided are imputed data.
CFS: corneal fluorescein staining; OSDI: ocular surface disease index questionnaire; VAS: global visual analogue scale assessment of ocular discomfort; n: number of patients.
[a] CFS responder: improvement of ≥2 points from Baseline in CFS in the analysis eye (i.e. change in CFS ≤-2).
[b] OSDI responder: improvement by ≥30% from Baseline in OSDI (i.e. % change ≤-30%).
[c] VAS responder: improvement by ≥30% from Baseline in global VAS assessment in the analysis eye.
[d] CFS-VAS responder: improvement of ≥2 points from Baseline in CFS and improvement by 30% or more from Baseline in global VAS assessment, both in the analysis eye.
[e] Complete corneal clearing: CFS=0 in the analysis eye.
[f] p-value for treatment effect in the logistic regression mode

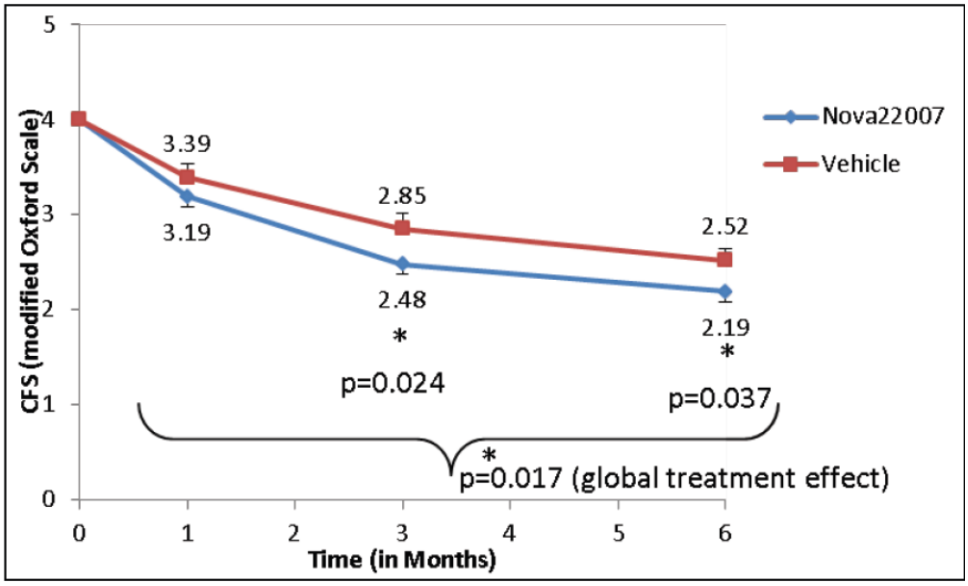
Other secondary efficacy endpoints

- Corneal Fluorescein Staining (CFS)

CFS score at Baseline was 4 in all FAS patients, in accordance with the inclusion criteria of the study protocol.

There was a statistically significant decrease (i.e. improvement) in CFS score over time (p<0.001) in the FAS. 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 as early as Month 3 (p=0.024), which was maintained at Month 6 (p=0.037). 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.

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).



CFS: corneal fluorescein staining; bars show standard errors.

Sample size at Month 1, 3 and 6: 149, 140 and 132 with NOVA22007, and 88, 89, 83 with vehicle.

Figure 2 - Mean CFS Scores from Baseline to Month 6 in the Analysis Eye (FAS)

- Ocular Surface Disease Index (OSDI) score

There was a clinically and statistically significant decrease in OSDI score over time in the FAS patients (p=0.003) compared to baseline, with no statistically significant difference between treatment groups. The improvement in OSDI score compared to Baseline was statistically significant as early as Month 1 in both treatment groups. At the Month 6 visit, the adjusted mean change in OSDI score from baseline was -13.6 with NOVA22007 and -14.1 with vehicle. The absence of a difference between NOVA22007 and vehicle was also found when adjusting for the average number of artificial tears used per day. Similar results were also found in the PPS.

- Visual Analogue Scale (VAS)

Mean (plus or minus SD) global VAS assessment score at Baseline was similar in both treatment groups (55.6±20.6 mm with NOVA22007 and 54.5±18.4 mm with vehicle).

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 decrease in the global VAS assessment score was statistically significant at Months 1, 3 and 6 in both treatment groups compared to Baseline. At Month 6, the adjusted mean change in global VAS assessment score from Baseline was -12.1 mm with NOVA22007 and -11.2 mm with vehicle. The absence of a difference between NOVA22007 and vehicle was also found when adjusting for the average number of artificial tears used per day.

- Schirmer Test (without anaesthesia)

Mean 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 ranged from 2.0 mm/5 min to 9.0 mm/5 min in both treatment groups and thus 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 compared to Baseline. At Month 6, the mean change in Schirmer test score from Screening (used as Baseline values in this test) 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.

- Use of Concomitant Artificial Tears

Median use of artificial tears was discussed by the applicant 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 of the study. 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).

Similar results were found in the PPS.

- Investigator Global Evaluation of Efficacy

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.

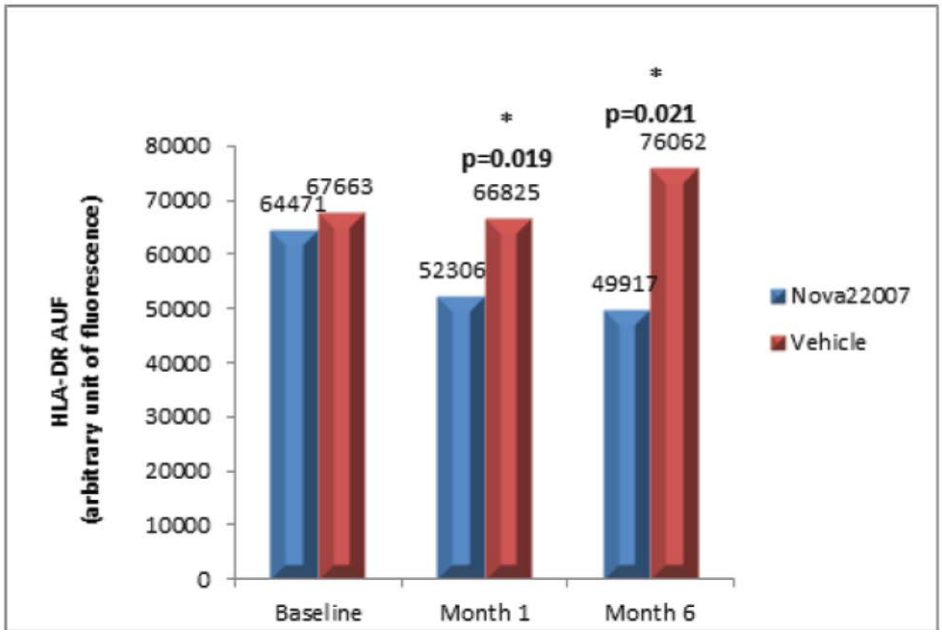
- HLA-DR Expression on the Conjunctival Cell Surface by Impression Cytology

At baseline, median HLA-DR (AUF) was relatively similar in both treatment groups (64471.0 AUF with NOVA22007 and 67663.5 AUF with vehicle). Values were spread over a large range in both treatment groups (6739 to 504052 AUF with NOVA22007 and 10117 to 477068 AUF with vehicle). The mean of the percentage of HLA-DR+ cells was similar in both treatment groups (71.5±17.9% with NOVA22007 and 73.3±14.2% with vehicle).

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.

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).

Similar results were found in the PPS.



Sample size at Baseline, Month 3 and 6: 119, 76 and 70 with NOVA22007, and 64, 42, 43 in vehicle.

Figure 3 – Median HLA-DR (AUF) from Baseline to Month 6 (FAS)

- Tear Break-Up Time (TBUT)

Mean 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. Similar results were found in the PPS.

- Lissamine Green Staining

During the 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. Mean 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. Similar results were found in the PPS.

- Quality of Life Questionnaires

National Eye Institute Vision Function Questionnaire

Mean NEI-VFQ-25 composite score at baseline was similar in both treatment groups (71.9±5.7 with NOVA22007 vs. 74.0±13.4 with vehicle). Similar results were also 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 individual scale scores revealed that at Baseline 7 out of 11 vision-specific items as well as the item "General health", which is not vision-specific, scored low (i.e. below 75/100 on average) in both treatment groups. All these items improved over 6 months in both treatment groups. 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), adjusted 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). Similar results were found in the PPS.

The EQ-5D questionnaire

Mean summary index of the EQ-5D questionnaire at Baseline was similar in both treatment groups (0.66±0.30 with NOVA22007 and 0.66±0.26 with vehicle). Mean 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 and no differences between treatments were found. Similar results were found in the PPS.

Ancillary analyses

(i) Post-hoc analyses

- CFS-OSDI Responders (based on at least 3 grades improvement in CFS) at Month 6

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.

Table 5 – CFS-OSDI response at month 6 (at least 3 grades CFS improvement) - FAS

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

CFS: corneal fluorescein staining; n: number of patients.
[a] 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).
[b] p-value for treatment effect in the logistic regression model.
[c] Total sample size for this analysis was 215 (132+83 patients), i.e. there were 30 missing data.

- CFS (At least 3 grades improvement) at Month 6

In the FAS and based on imputed data (according to the randomised 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 using observed data. A total of 47 patients (35.6%) receiving NOVA22007 and 12 patients (14.5%) receiving vehicle showed a positive CFS response at Month 6. The difference between groups was statistically significant (p=0.001).

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

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

CFS: corneal fluorescein staining; n: number of patients.
a 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).
b p-value for treatment effect in the logistic regression model.
c Total sample size for this analysis was 215 (132+83 patients), i.e. there were 30 missing data.

- CFS-OSDI responder rate (primary efficacy variable) over time, Repeated Measures Analysis

Based on observed data, the CFS-OSDI responder rate increased over time in the FAS 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). This difference between treatments was not confirmed in the PPS, although the p value was almost statistically significant (p=0.052).

- Worst Tear Film Osmolarity (Between Both Eyes) in Patients with Elevated Tear Film Osmolarity at Baseline

At Baseline, 55 patients had at least one eye with a tear film osmolarity higher than 308 mOsms/L including 34 patients (22.1%) in the NOVA22007 group and 21 patients (23.1%) in the vehicle group. Mean values for worst tear film osmolarity at baseline were similar in both treatment groups (331.0±20.2 mOsms/L with NOVA22007 and 321.5±10.5 mOsms/L with vehicle). There was a decrease (i.e. improvement) in worst tear film osmolarity over time in both treatment groups, whereby the NOVA22007 group showed a statistically significantly greater change from Baseline to Month 6 than the vehicle group (p=0.048). 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. 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 for defining an underlying inflammation) at Month 6, whereas they remained slightly higher than 308 mOsms/L in the vehicle group.

(ii) Descriptive Efficacy Analyses - Part 2 of SANSIKA (FAS-OPEN)

Among the 208 patients who completed part 1 of SANSIKA, 207 entered part 2 and all received NOVA22007, allowing a descriptive analysis of the long-term efficacy of NOVA22007 over 12 months.

The CFS-OSDI responder rate continued to increase during the last 6 months of the study in both groups to reach 39.1% at Month 12 in the NOVA22007/NOVA22007 group (patients who received NOVA22007 for 12 months) and 38.0% in the vehicle/NOVA22007 group (patients who received the vehicle for 6 month and were then switched to NOVA22007).

The other responder rates (CFS, OSDI, VAS and CFS-VAS) also increased between Month 6 and Month 12, with no marked differences between groups except the CFS responder rate which was higher in the NOVA22007/NOVA22007 group (65.6%) compared to the vehicle/NOVA22007 group (54.4%) at Month 12. Catching up in the vehicle/NOVA22007 group during the last 6 months was also observed for complete corneal clearing (11.4% at Month 12, versus 12.5% in the NOVA22007/NOVA22007 group), the investigator's global evaluation of efficacy at Month 12 (71.7% of patients showing a satisfactory/very satisfactory improvement in the NOVA22007/NOVA22007 group vs. 69.9% in the vehicle/NOVA22007 group), and HLA-DR expression. During the last 6 months of the study, median HLA-DR level of expression (AUF) decreased in the vehicle/NOVA22007 group (-5065.5 AUF), whereas it did not change in the NOVA22007/NOVA22007 group (+314.0 AUF).

Mean scores of CFS, OSDI and global VAS decreased (i.e. improved) steadily between baseline and Month 12 in both group. The improvement was greater during the first 6 months than during the last 6 months. Mean lissamine green total score decreased (i.e. improved) between baseline and Month 6, then remained stable until Month 12, in both treatment groups.

Other variables (Schirmer test, TBUT and NEI-VFQ-25 and EQ-5D) remained relatively stable in both treatment groups. In addition, the percentage of HLA-DR+ cells varied over time but did not markedly differ between baseline and Month 12 in both groups. The analysis of the use of AT and tear film osmolarity was hampered by the low sample size for both variables.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 7 – Summary of Efficacy for SANSIKA

Title: 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 CYCLOKAT 1mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe dry eye disease (DED)			
Study identifier	NVG10E117		
Design	Multicentre, randomised, double-masked, parallel group, vehicle-controlled Phase III clinical trial (part 1) with open label follow-up (part 2)		
	Duration of main phase:		6 months (part 1)
	Duration of Run-in phase:		1-2 weeks washout (artificial tears)
	Duration of Extension phase:		6 months open label follow-up
Hypothesis	Superiority (active vs. vehicle)		
Treatments groups	NOVA22007 0.1%		One drop of cyclosporine 1mg/mL (0.1%) eye drops once daily at bedtime for 6 months, N=154
	Vehicle		One drop of vehicle eye drops once daily at bedtime for 6 months, N=91
Endpoints and definitions (only selected endpoints are presented)	Primary endpoint	CFS-OSDI composite responder rate	A responder was defined as a patient satisfying the following conditions simultaneously: change from baseline in CFS ≤-2 and in OSDI ≤-30% at month 6
	Secondary endpoint	CFS responder ≤-2 steps	A responder was defined as a patient with a change from baseline in CFS ≤-2 at month 6
	Secondary endpoint	CFS score over time	CFS using the modified Oxford scale at month 1, 3 and 6
	Secondary endpoint	OSDI score over time	OSDI (cornea only) at month 1, 3 and 6
	Other endpoint	HLA-DR	Change in HLA-DR expressions quantified in Arbitrary Units of Fluorescence [AUF]
Database lock	6 month, 12 month		

Results and Analysis

Analysis description	**Primary Analysis:** The primary analysis was performed on the full analysis set (FAS) using imputed data and based on a logistic regression model.		
Analysis population and time point description	Intent to treat: All patients randomized into the study that received any amount of the study drug (FAS). Time points: Month 6 or Month 1, 3 and 6 if measurement over time		
Descriptive statistics and estimate variability	Treatment group	NOVA22007 0.1%	Vehicle
	Number of subject	154	91
	Primary endpoint: CFS-OSDI composite responder rate, responders n (%)	**44 (28.6%)**	**21 (23.1%)**
	CFS responder rate (≤-2 steps), responders n (%)	80 (51.9%)	41 (45.1)

	CFS score over time, mean change from Baseline	Month 1: -0.81 Month 3: -1.52 Month 6: -1.81	Month 1: -0.61 Month 3: -1.15 Month 6: -1.48
	Standard deviation (SD)	Month 1: 0.98 Month 3: 1.25 Month 6: 1.27	Month 1: 0.88 Month 3: 1.24 Month 6: 1.08
	OSDI score over time, mean change from Baseline	Month 1: -9.66 Month 3: -12.10 Month 6: -14.41	Month 1: -8.54 Month 3: -11.96 Month 6: -13.33
	SD	Month 1: 17.41 Month 3: 20.40 Month 6: 21.12	Month 1: 18.65 Month 3: 19.33 Month 6: 18.80
	HLA-DR expression [AUF], mean change from baseline	Month 1: -35564.4 Month 6: -50307.1	Month 1: -8785.2 Month 6: -14365.2
	SD	Month 1: 80400.1 Month 6: 96794.8	Month 1: 64390.2 Month 6: 69023.6
Effect estimate per comparison	**Primary endpoint: CFS-OSDI composite responder rate**	**Comparison groups**	**NOVA22007 0.1% vs. vehicle**
		Absolute difference in responder rate	**5.5%**
		P-value	**0.326**
	CFS responders ≤-2 steps	Comparison groups	NOVA22007 0.1% vs. vehicle
		Absolute difference in responder rate	6.8%
		P-value	0.346
	CFS score over time, change from baseline	Comparison groups	NOVA22007 0.1% vs. vehicle
		Difference in mean change from baseline	Month 1: -0.2 Month 3: -0.37 Month 6: -0.35
		P-value	Month 1: 0.095 Month 3: 0.024 Month 6: 0.037 Global: 0.017
	OSDI score over time, change from baseline	Comparison groups	NOVA22007 0.1% vs. vehicle
		Difference in mean change from baseline	Month 1: 2.21 Month 3: 2.65 Month 6: 2.61
		P-value	Month 1: 0.705 Month 3: 0.808 Month 6: 0.858 Global: 0.969
	HLA-DR expression	Comparison groups	NOVA22007 0.1% vs. vehicle
		Difference in mean change from baseline	Month 1: 26779.2 Month 6: 35941.9
		P-value	Month 1: 0.019 Month 6: 0.021
Analysis description	**Secondary Analysis:** Repeated measures analysis of variance (ANOVA) was applied on the full analysis set (FAS) for the secondary analysis of CFS and OSDI scores.		

2.5.2.1. Analysis performed across trials (pooled analyses and meta-analysis)

A meta-analysis of the data from the two Phase III trials SANSIKA and SICCANOVE was performed by the applicant. The SICCANOVE study is described in section 2.5.2.3.

The primary objective of the meta-analysis was to increase the precision of the estimate of the magnitude of the treatment effect. The second objective was to deepen the scientific knowledge of the disease in patients with Sjögren syndrome, and on HLA-DR expression.

The meta-analysis used the same endpoint, analysis, and methodology as in the SANSIKA study and focused on composite CFS/OSDI response at Month 6:

- In the combined FAS population (n=734), i.e. all FAS SANSIKA (n=245) and SICCANOVE patients (n=489), to avoid the bias due to the post-hoc selection of the most responsive patients from SICCANOVE.
- In the population with severe DED only (severe FAS), i.e. those patients with a CFS graded 4 on the modified Oxford grading scale, and OSDI ≥23, as included in the SANSIKA study; this patient population only represented a subset of the patient population included in the SICCANOVE study (NOVA22007 n=39; vehicle n=35).

A specific meta-analysis model was used for the data analysis. The study effect was included in a logistic model to take into account the structure of the data set (test and estimation of heterogeneity between studies). There was no adjustment for multiplicity; statistical testing was performed at a two-tailed significance level of 0.05.

Results

- CFS-OSDI response at Month 6

In the combined FAS population, the rate of responders (patients with an improved CFS ≥2 and an improved OSDI ≥30%) was greater with NOVA22007 compared to vehicle with a statistically significant difference (p=0.015). A similar significant difference was observed in the severe combined population (p=0.038).

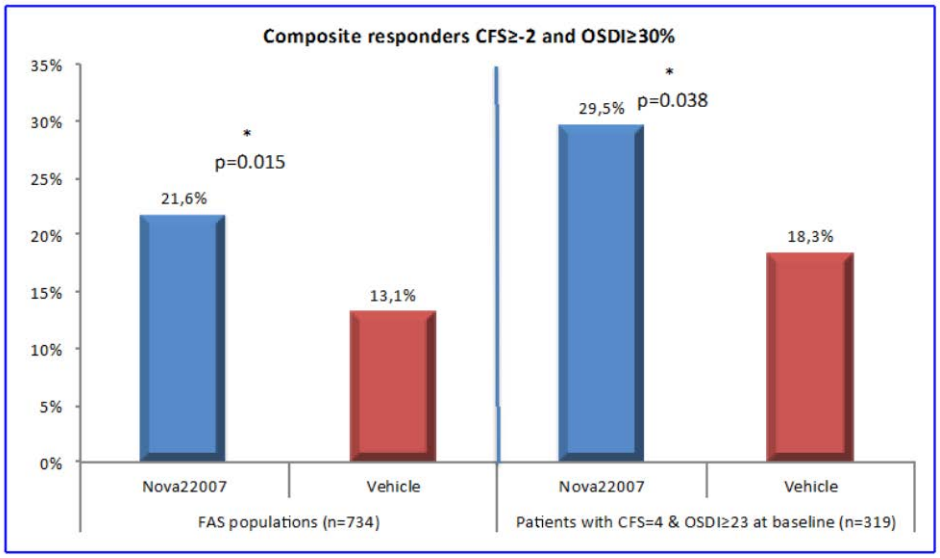


Figure 4 – Meta-analysis of composite CFS/OSDI response (All FAS and Severe FAS)

Sjögren patients

In the subgroup of Sjögren patients with severe DED (CFS graded 4 and OSDI ≥ 23, n= 130), the rate of responders was 23.4% for NOVA22007 and 9.4% for vehicle (p=0.036), resulting in an Odds-Ratio of 3.04 [1.13; 9.50]. In the Sjögren All FAS, the rate of responders was 19.2% for NOVA22007 and 11.6% for vehicle resulting in an Odd-Ratio of 1.773 [0.893; 3.657]. The between-treatment difference was not statistically significant.

- HLA-DR expression on the conjunctival cell surface by impression cytology

Impression cytology was performed in all patients involved in the Phase III SANSIKA pivotal study and in a subset (n= 70) of the patients of the Phase III SICCANOVE supportive study. HLA-DR expression was measured at Months 1, 6 and 12 in SANSIKA, and at Month 6 in SICCANOVE. Data of the patients included in the meta-analysis were distributed according to the level of disease severity, meaning by CFS grade severity from 2 to 4 inclusive. Data from Baseline and Month 6 were pooled in the meta-analysis.

At baseline, inflammation appeared higher in Grade 4 patients as compared to Grade 3 or 2, as shown by the mean values of HLA DR expression. At Month 6 and as compared to vehicle, NOVA22007 significantly reduced the HLA DR expression (p<0.001).

2.5.2.2. Clinical studies in special populations

In addition to the data included and assessed in the pre-specified meta-analysis (see section 2.5.2.1.), post hoc subgroup analyses were performed on a purely descriptive basis. Data were presented for the change in CFS score in the All FAS population according to age, gender, menopausal and Sjögren status, age and duration of the disease. Results are displayed using a Forest plot (see Figure 5).

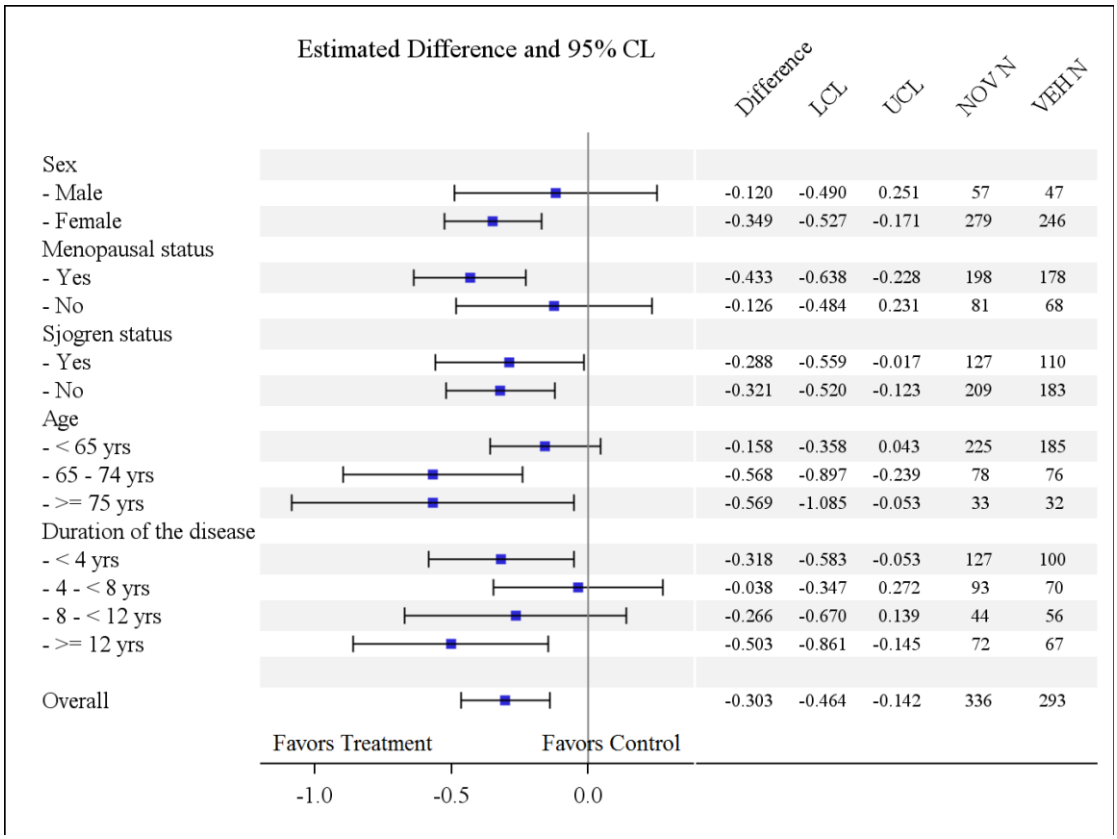


Figure 5 – Change from Baseline in CFS score (All FAS)

2.5.2.3. Supportive study(ies)

The phase II studies N09F0502 and NVG08B112 (ORA) are described in section 2.5.1. A summary of the supportive Phase III trial SICCANOVE is given below.

Study NVG06C103 (SICCANOVE): A Phase III, multicenter, randomised, controlled, double-masked trial of NOVA22007 (ciclosporin 0.1%) ophthalmic cationic emulsion versus vehicle in patients with moderate to severe dry eye syndrome.

Study design and objectives:

The Phase III supportive SICCANOVE study enrolled patients with moderate to severe DED from 61 European centres in Germany, Italy, Czech Republic, Spain and the UK. Apart from the disease severity, inclusion/exclusion criteria were broadly comparable to SANSIKA.

The **inclusion criteria** are listed below:

Male or female patients, aged ≥18 years, who had moderate to severe dry eye condition at Baseline persisting despite conventional management (which could include artificial tear drops, gels or ointments and punctual occlusion), defined as follows:

- 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 (TBUT) ≤8 seconds, and,
- CFS ≥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).

This study consisted of three phases: Screening, a 2-week wash-out period (between Screening and Baseline visits), and a 6-month double-masked treatment phase (Baseline to Month 6 visits).

The study was designed to primarily demonstrate the **superiority of NOVA22007 0.1% ophthalmic emulsion, administered once daily versus vehicle after a 6-month treatment period** (last patient last visit on 8 September 2009). Randomisation was centralised and stratified by Sjögren syndrome status.

Use of artificial tears was allowed but their intake was capped to no more than one drop, six times daily, in each eye, during the entire study period.

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

- Objective parameter: Change in corneal fluorescein staining (modified Oxford scale) from Baseline to Day 168.
- Subjective parameter: Change in global score of ocular discomfort unrelated to study medication instillation (VAS), from Baseline to Day 168.

Assessment of efficacy was made only with the "worst eligible eye", which 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.

Analyses were performed on the FAS (all randomised patients except for those who withdrew from the study prior to providing any post-treatment efficacy evaluations unless they withdrew for a reason clearly related to study treatment) 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). No adjustments for multiplicity were necessary since statistical significance for both co-primary variables at the same significance level (5%) was required. Missing data for the primary efficacy variables were to be imputed by the last available value (which may have been the Baseline value). In addition, secondary analyses were performed in the PP population, based on the ANCOVA model as described above with country effect, using the observed data only and with handling of missing data by the best plausible outcome.

Relevant secondary endpoints are described under results.

The efficacy variables used in SICCANOVE were largely the same as in SANSIKA (see also section 0).

Results

Six hundred (600) patients were screened and 496 patients were enrolled. Of these, 7 patients were excluded from the FAS population and the FAS population consisted of 489 patients. Of these, 241 patients received NOVA22007 treatment and 248 patients vehicle. There were 142 patients in the FAS population who had a major protocol deviation that may have had an impact on the efficacy analysis for the two co-primary endpoints. These patients were excluded from the PP population. Thus, the PP population consisted of 347 patients.

Demographic and baseline disease characteristics were well balanced between the two treatment groups. Overall, there were 76 male (15.5%) and 413 female (84.5%) patients included in the study. The distribution of male and female patients was similar between treatment groups and the majority of female patients were post-menopausal (294/413 [71.2%]). Patients had a mean age comparable between the treatment groups (57.6 years vs. 58.8 years) and age ranged from 20 to 90 years. The majority of patients included in the study 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%). A total of 177/489 patients (36.2%) had Sjögren's syndrome and the distribution of Sjögren's syndrome patients was similar between treatment groups.

- Co-primary efficacy endpoint

The mean change in CFS from Baseline to Day 168 was -1.05 (NOVA22007) and -0.82 (vehicle). A statistically significant treatment effect in favour of NOVA22007 was shown using an ANCOVA model (p=0.009). These findings were supported by a non-parametric analysis and in the PP population and in all the predefined robustness analyses.

With regards to the country effect, the estimated treatment difference between groups was (not significantly) in favour of vehicle only in two countries (Czech Republic and UK), which was suggested to be due to a patient population with less severe dry eye syndrome at Baseline (Czech Republic) and the high number of patients with blepharitis in the UK, as it has been shown that ciclosporin has merely a modest effect in DED patients with blepharitis. The treatment by Sjögren status interaction was not statistically significant (p=0.599). However the Sjögren effect (alone) is significant in all models: patients with Sjögren syndrome have an evolution of CFS different from the other patients, but independently of their group of treatment.

The mean change in global ocular discomfort VAS score from Baseline to Day 168 was -12.82 (NOVA22007) and -11.21 (Vehicle) showing a noticeable improvement in both groups. No statistically significant difference between treatment groups was shown using an ANCOVA model (p=0.808) for this subjective endpoint. Similar results were shown in the PP population.

- Secondary efficacy endpoints

The mean change in CFS score from Baseline to Day 28 was -0.77 and -0.52 for the NOVA22007 and vehicle groups, respectively. 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 was shown at both Day 28 (p=0.002) and Day 84 (p=0.030), which indicates that the improvement in the objective sign is present as early as Month 1 of treatment.

The change in lissamine green staining (Van Bijsterveld scale) of the interpalpebral conjunctiva from Baseline were slightly greater for the NOVA22007 group versus vehicle at Day 28 (-1.52 vs. -1.30), Day 84 (-2.12 vs. -1.74) and Day 168 (-2.37 vs. -2.18). A statistically significant treatment effect in favour of NOVA22007 was shown for the global effect of treatment, following a repeated measures ANCOVA (p=0.048).

The percentage of responders in ocular symptoms (defined as a decrease of at least 25% in ocular discomfort VAS score) was 40.66% for the NOVA22007 group vs. 39.11% for the vehicle group at Day 28, 48.13% vs. 45.97% at Day 84, and 50.21% vs. 41.94% at Day 168. The difference in favour of NOVA22007 at Day 168 was statistically significant (p=0.048).

Individually, ocular discomfort symptoms unrelated to study medication were not statistically significantly different between treatment groups, with the exception of burning/stinging score (p=0.038 in favour of the vehicle group). The PP population supported the results of the Full Analysis Set.

No statistically significant difference was observed between groups for Schirmer's tear test score, TBUT, complete responders in CFS, OSDI score, and overall evaluation of efficacy by the investigator.

- Post-hoc analyses

Patients with CFS ≥ 3 and OSDI score ≥ 23 at baseline

This population represented 50% of the overall study population (n=246). Statistically significant between-group differences in favour of NOVA22007 were observed in the following clinical parameters:

- The percentage of responders in CFS (improvement of at least 2 grades), p=0.047.
- The percentage of co-responders on both sign (improvement of at least 2 grades in CFS) and symptom (improvement of 30% OSDI score), p=0.049.
- The percentage of co-responders on both sign (improvement of at least 2 grades in CFS) and symptom (improvement of 7.3 points in patients with OSDI at baseline between 23 and 32 AND 13.4 points improvement in patients with OSDI at baseline ≥33), p=0.013.

Patients with CFS equal to 4 at baseline

Patients with severe dry eye disease, defined as having a grade 4 at baseline, represented 17% of the overall population at baseline (n=85). Superiority of NOVA22007 over vehicle was observed for the change in CFS compared to Baseline, which was -1.47 (NOVA22007) and -0.69 (vehicle) (p=0.002), as well as with regards to the percentage of co-responders on both signs (improvement of at least 2 grades in CFS) and symptoms (improvement of 30% OSDI score) with 32.56% for IKERVIS versus 7.14% for vehicle (p=0.003). Statistically significant between-group differences in favour of NOVA22007 were furthermore observed for the following clinical parameters:

- Change in lissamine green staining (p= 0.003).
- Change in corneal Schirmer's tear test (p=0.047).
- Percentage of responders in CFS (at least 2 grades improvement) (p=0.011).
- Percentage of co-responders on both sign (improvement of at least 2 grades in CFS) and symptom (OSDI improvement of at least 13 points) (p=0.015).

Patients with a CFS equal to 2 at baseline

This moderate patient population represented 36% of the overall population at baseline (n=178). Statistically significant between-group difference in favour of NOVA22007 was observed in the percentage of complete CFS responders (i.e. CFS score of "0" on the modified Oxford scale) (p=0.028).

2.5.3. Discussion on clinical efficacy

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

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

Design and conduct of clinical studies

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

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

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

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

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

Efficacy data and additional analyses

- **Dose selection**

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

Taking into account all available information, the CHMP agreed that the 0.1% dose strength seemed to have shown the most consistent improvements. A BID dosing was not expected to provide additional benefit, but may lead to compliance issues due to pain and irritation at site instillation.

- **Clinical efficacy**

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

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

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

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

Amongst the post-hoc analyses, tear film osmolarity in patients with an osmolarity level >308 mOsms/L at Baseline, a threshold known to be indicative of DED, improved significantly more in patients treated with IKERVIS than in the vehicle group (p=0.048). However, the CHMP noted the limited evidence that can be obtained from data derived post-hoc.

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

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

When comparing the two studies, the CHMP noted that the vehicle response was substantially greater in SANSIKA compared to SICCANOVE. From the post hoc analysis in severely affected patients in SICCANOVE, an effect size of about 7% had been expected in the vehicle group for the CFS-OSDI responder rate. This could not be reproduced in SANSIKA where the treatment effect in the vehicle group was much higher with 23%. The applicant suggested that this might have been due to various factors, such as the heterogeneity and complexity of the disease, the poor correlation between signs and symptoms, the choice of the responder definition, and the optimisation of the IKERVIS formulation. While in SICCANOVE the former BAK formulation was used, the formulation in SANSIKA contained CKC as an excipient. The BAK formulation contained a higher concentration of quaternary ammonium compounds which might have caused ocular irritation. Whether this change contributed to the difference in the study findings was not clear. Furthermore, it could not be excluded with certainty that the ad libitum use of artificial tears in SANSIKA as opposed to the capped use of artificial tears allowed in SICCANOVE may have had an impact on the patients' subjective symptoms even with existing corneal erosion, which in turn might have confounded the results towards an increased effect size in patients in the vehicle arm in SANSIKA.

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

Importantly, the phase III studies did not demonstrate a beneficial effect of IKERVIS compared to vehicle on symptoms. This finding was complemented by the lack of a significant effect with regards to use of artificial tears and quality of life. However, in order to demonstrate efficacy in DED, generally a significant effect on both signs and symptoms or at least a significant effect in signs or symptoms and a strong trend for the other parameter would be preferred. The difficulty in establishing such combined effect was acknowledged by the CHMP as it was well known that signs and symptoms of DED poorly correlate and that some patients with a low degree of ocular surface damage experience severe symptoms, while others with substantial corneal lesions don't. One reason

may be that advanced forms of DED with a high degree of ocular surface damage may cause reduced corneal sensation. Another reason could be a delay in the improvement of symptoms. Some support for a lag time effect on symptoms was provided by a post-hoc analysis presented by the applicant during an oral explanation. When testing the correlation (Spearman) between the change in CFS (signs) and OSDI (symptoms score) over time, the correlation increased slightly from month 1 through to month 6, thus suggesting that an improvement in signs may indeed with time result in an improvement in symptoms. However, the correlation was overall weak and was considered inconclusive.

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

Additional expert consultation

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

Question 1.

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

The expert panel highlighted that DED is a multifactorial disease that, despite different possible triggers and aetiologies, is based on a common underlying vicious circle of factors including inflammation, which are inter-dependent and contribute to disease maintenance and progression. Both an improvement in signs and a relief in symptoms are important treatment objectives in DED. However, there is no clear correlation between signs and symptoms, in particular in severe forms of DED, where multiple factors including a potential loss in ocular surface sensitivity influence the symptomatology and so individual patients may suffer from pronounced pain and irritation while others experience less severe symptoms. As a result, it has proven difficult to demonstrate an effect of a medicinal product on both signs and symptoms and no such product is yet available. The clinicians also discussed that an improvement in signs could lead to a reduction of symptoms in the longer term (possibly several years), once damaged cells and tissues had sufficient time to recover. However, such correlation has not been demonstrated to date.

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

Question 2.

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

- *Change in Corneal Fluorescein Staining (CFS) score using the Modified Oxford Scale: Over the 6-month treatment period in SANSIKA, a global effect of treatment in favour of IKERVIS over vehicle was observed (p=0.017). At the end of Part 1 of the study (Month 6 Visit), the adjusted mean change in CFS score from baseline was -1.76 with IKERVIS and -1.42 with vehicle (p=0.037), resulting in a between-treatment difference of 0.35.*
- *The decrease in HLA-DR level of expression (AUF) from baseline was greater with IKERVIS than with vehicle, with a statistically significant difference at Month 1 (p=0.019) and Month 6 (p=0.021).*

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

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

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

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

Question 2a.

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

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

Question 2b. and c.

There was agreement amongst the experts, that effective treatment of severe keratitis and repair of epithelial damage, as can be measured by corneal staining, can prevent serious complications in DED including pronounced and permanent damage of the ocular surface and function. However, the treatment effect would

have to be sufficiently large to prevent worsening of the disease. In line with question 2a, the experts expressed different views on the relevance of the observed effects of IKERVIS.

Question 2d.

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

Question 3.

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

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

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

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

2.5.4. Conclusions on the clinical efficacy

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

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

2.6. Clinical safety

Safety has been evaluated in four studies, two phase II studies including patients with moderate to severe DED or mild to moderate DED, respectively, and 2 phase III studies (SANSIKA and SICCANOVE), including patients with moderate to severe DED or severe DED, respectively.

Safety data were pooled based on the safety populations of each of the individual studies. These included all randomised patients who received at least one dose (1 drop once daily) of IKERVIS 0.1%. Two different analysis cohorts were used:

- The Double Masked Cohort (n= 396) including all patients from the 6-month double masked phases of the SICCANOVE and SANSIKA studies allowing a comparison of the extent of safety issues for IKERVIS versus vehicle.
- The All Studies Cohort (n= 520) combining data from the 2 phase III studies (396 patients) including (i) the 6 month open label safety follow up, where all patients from the vehicle group (79 patients) received IKERVIS 0.1% and (ii) the Phase IIb (ORA) study, taking into account only patients (45 patients) exposed to IKERVIS 0.1%, 1 drop once daily. The Phase IIa study was not included in this cohort due to the use of a different dose regimen (BID instead of QD).

Patient exposure

Overall, 602 patients were exposed to IKERVIS at any dose for up to 12 months in clinical trials (see Table 8). Twelve (12) subjects have been exposed to IKERVIS 0.025% for a maximum of 3 months, and 58 to IKERVIS 0.05% for a maximum of 3 months. In the phase II trials 57 persons were exposed to IKERVIS 0.1% for up to three months. In two phase III trials 396 patients were exposed to IKERVIS 0.1% for at least 6 months and 114 for at least 12 months.

The mean exposure to IKERVIS 0.1% and vehicle during the double masked period was 153.9 days ± 49.9 and 158.5 ± 44.8 days, respectively. The mean exposure to IKERVIS 0.1% in the all studies cohort was 191.5 ± 106.3 days.

Table 8 – Exposure to IKERVIS by clinical study

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
N09F0502 (IIA)	38	38	12	0 **
NVG08B112 (ORA) (IIB)	89	89	45	0 **
SICCANOVE (III)	246	242	242	204 (completed 6 months)
SANSIKA (III) Part 1	154	154	154	129 (completed 6 months)
SANSIKA (Part 2)	207	207	207	114 (completed 12 months)

	63 (completed 6 months)

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

** Subjects in the phase II studies had a maximum exposure of 3 months.

Patients receiving IKERVIS 0.1% QD were predominantly female (439; 84.4%), and most of them (71.3%) were postmenopausal. The mean age was 59.3 years (±13.3) with about 64.8 % of patients aged less than 65 years and about 12% being older than 75 years. Regarding the severity of the disease, 53.5% of patients (278) presented with severe DED, defined by a CFS staining grade of 4 and 5. One third of the patients (34.6%) had Sjögren syndrome. The majority of patients were Caucasians. Only 4 Black/Afro-American patients and no Asian patients received IKERVIS.

Adverse events

In the Double Masked Cohort, (combined phase III studies over a 6 month period), 382 (51.9%) patients had a Treatment Emergent Adverse Event (TEAE). Of these, 221 patients received IKERVIS 0.1% (55.8%) and 161 (47.4%) vehicle (see Table 9 for an overview of TEAEs in the Double Masked Cohort). Patients may have had more than one TEAE. The percentage of patients with a drug related TEAE was 35.9% for IKERVIS 0.1% and 20.3% for the vehicle group. A higher rate of patients with a severe drug related TEAE (21.7%) was reported for the IKERVIS group compared to the vehicle group (10.6%).

In the All Studies Cohort, a total of 308 (59.2%) patients had a TEAE and 204 (39.2%) had a TEAE that was considered related to study medication. This incidence was comparable as the one observed on the 6-month Double-Masked Cohort.

The most common TEAEs experienced by patients occurred mainly in the system organ classes (SOC) ‘eye disorders’ and ‘general disorders and administration site conditions’. The proportion of TEAEs was higher in the IKERVIS group compared to vehicle.

Table 9 – Overview of TEAEs in the Double Masked Cohort

Categories	NOVA2200 0.1% N=396	Vehicle N=340	Risk Ratio [95% CI]
All TEAEs	221 (55.8)	161 (47.4)	1.179 [1.022: 1.359]
Drug-related TEAEs	142 (35.9)	69 (20.3)	1.767 [1.378: 2.265]
Severity of TEAEs			
- Mild	75 (18.9)	56 (16.5)	1.150 [0.840: 1.575]
- Moderate	48 (12.1)	50 (14.7)	0.824 [0.570: 1.192]
- Severe	98 (24.7)	52 (15.3)	1.618 [1.195: 2.192]
- Unknown	-	3 (0.9)	
Severity of drug-related TEAEs			
- Mild	39 (9.8)	22 (6.5)	1.522 [0.921: 2.515]
- Moderate	17 (4.3)	12 (3.5)	1.216 [0.589: 2.510]
- Severe	86 (21.7)	35 (10.3)	2.110 [1.464: 3.040]
Death	-	-	
SAE	15 (3.8)	16 (4.7)	0.805 [0.404: 1.604]
Drug-related SAE	1 (0.3)	1 (0.3)	0.859 [0.054: 13.67]
Discontinuation due to AE	48 (12.1)	35 (10.3)	1.177 [0.781: 1.776]
Discontinuation due to drug-related AE	37 (9.3)	23 (6.8)	1.381 [0.838: 2.277]

n (%): number and percentage of patients.
A subject is counted only once in his/her maximal severity.

See Table 10 for an overview of the most common TEAEs observed (based on the All Study Cohort).

Table 10 – Most common TEAEs (>1%) in any treatment group – All Study Cohort

Body system (n, %)	PT name	NOVA22007 0.1% N=520
Cardiac disorders		5 (1.0)
Eye disorders		**142 (27.3)**
	Blepharitis	7 (1.3)
	Conjunctival hyperaemia	13 (2.5)
	Conjunctivitis	2 (0.4)
	Dry eye	6 (1.2)
	Erythema of eyelid	10 (1.9)
	Eye irritation	49 (9.4)
	Eye pain	20 (3.8)
	Eye pruritus	5 (1.0)
	Eyelid oedema	7 (1.3)
	Keratitis	6 (1.2)
	Lacrimal disorder	13 (2.5)
	Lacrimation increased	12 (2.3)
	Meibomianitis	14 (2.7)
	Ocular hyperaemia	12 (2.3)
	Photophobia	6 (1.2)
	Vision blurred	7 (1.3)
	Visual acuity reduced	10 (1.9)
Gastrointestinal disorders		14 (2.7)
General disorders and administration site conditions		**133 (25.6)**
	Instillation site erythema	10 (1.9)
	Instillation site irritation	47 (9.0)
	Instillation site lacrimation	15 (2.9)
	Instillation site pain	85 (16.3)
Infections and infestations		64 (12.3)
	Influenza	2 (0.4)
	Nasopharyngitis	15 (2.9)
	Sinusitis	6 (1.2)
	Urinary tract infection	7 (1.3)
Injury, poisoning and procedural complications		15 (2.9)
Investigations		15 (2.9)
	Blood pressure systolic increased	3 (0.6)
	Intraocular pressure increased	5 (1.0)
Musculoskeletal and connective tissue disorders		20 (3.8)
	Back pain	6 (1.2)
Nervous system disorders		18 (3.5)
	Headache	9 (1.7)
Psychiatric disorders		6 (1.2)
Respiratory, thoracic and mediastinal disorders		9 (1.7)
	Cough	2 (0.4)
Skin and subcutaneous tissue disorders		13 (2.5)
Vascular disorders		13 (2.5)
	Hypertension	9 (1.7)

n (%): number and percentage of patients.
MedDRA ver. 14.1
Patients receiving NOVA22007 in Vehicle/NOVA22007 group of NVG10E117 (Open phase) study were included in NOVA22007 0.1% group.

- Ocular TEAEs

Overall (All Study Cohort), a total of 243 patients (46.7%) experienced ocular TEAEs. Of these, 38.7% (201 patients) were considered by the investigator as drug related ocular TEAEs and 17.7% (92 patients) experienced severe drug related ocular TEAEs.

When comparing the frequency between treatment groups (Double Masked Cohort), ocular TEAEs were reported in a higher proportion of patients treated with IKERVIS (42.7%) than with vehicle (27.6%). Ocular TEAEs were considered by the investigator to be treatment related in a higher proportion of patients (35.1%) treated with IKERVIS 0.1% than with vehicle (17.6%). Ocular drug related TEAEs, as judged by the investigator, were more severe in IKERVIS group (21.7%) than the vehicle group (10%). Two patients (one receiving IKERVIS and the other vehicle) reported serious ocular AEs that were considered as drug related. Forty-two (10.6%) patients discontinued to an ocular TEAE versus 7.1% of patients in the vehicle group. Of these, 9.3% (37 patients) discontinued to drug related ocular TEAE versus 5.9% (20 patients) in the vehicle group. The most common AEs reported in the vehicle group were eye pain (13 patients, 3.8%), meibomianitis (12 patients, 3.5%) and visual acuity reduced (12 patients, 3.5%).

The most frequently reported ocular TEAEs assessed by the investigator as having at least a possible relationship to IKERVIS (All Study Cohort) were instillation site pain (16%), instillation site irritation (9%), eye irritation (8.8%), eye pain (3.5%), instillation site lacrimation (2.9%), lacrimation increased (2.1%), instillation site erythema (1.9%), ocular hyperaemia (1.9%), conjunctival hyperaemia (1.7%), erythema of eyelid (1.7%), eyelid oedema (1.3%), and vision blurred (1.2%). Uncommon ocular TEAEs for which a relationship to IKERVIS could not be excluded were keratitis bacterial, herpes zoster ophthalmic, conjunctival oedema, lacrimal disorder, eye discharge, eye pruritus, conjunctival irritation, conjunctivitis, foreign body sensation in eyes, deposit eye, keratitis, blepharitis, corneal decompensation, chalazion, corneal infiltrates, corneal scar, eyelid pruritus, and iridocyclitis as well as instillation site reaction, instillation site discomfort, instillation site pruritus and instillation site foreign body sensation.

- Systemic TEAEs

Systemic TEAEs were reported in 146 patients (28.1%) in the All Study Cohort. Systemic TEAEs were reported in similar proportions in the IKERVIS 0.1% and vehicle treatment groups (24.5% versus 28.2%, Double-Masked Cohort). A total of 3.5% of these events were considered by the investigator drug related systemic TEAEs in the IKERVIS group and 4.4% in the vehicle group. Most of the systemic TEAEs were mild to moderate. No serious drug related systemic TEAE was reported. The most frequently systemic drug related AEs reported were headache.

- Comparative safety of BAK and CKC formulations

During the development programme for IKERVIS, the formulation of the drug product was changed in terms of excipient from benzalkonium chloride (BAK, 0.02% w/w) to cetalkonium chloride (CKC, 0.005% w/w). BAK containing product was used in the SICCANOVE study and the phase IIa study. The CKC containing product was used in SANSIKA and the phase IIb study.

In general the incidence of TEAEs were similar in the SICCANOVE and SANSIKA studies apart from a lower incidence of severe ocular TEAEs in those exposed to CKC (SANSIKA) compared to BAK (SICCANOVE). Rates of discontinuation due to ocular TEAEs were similar between the studies.

Serious adverse event / deaths / other significant events

There were no deaths reported in any of the studies.

In the phase III studies (Double-Masked Cohort), 31 (4%) patients had a SAE during the initial 6 months period including 15 (3.8%) in the IKERVIS group and 16 (4.7%) in the vehicle group. Two patients (0.3%) had an SAE considered to be drug related, of which one was considered related to IKERVIS (epithelial erosion of the cornea). The other one was related to the vehicle (reduced visual acuity). The IKERVIS related AE was a case of severe epithelial erosion of the cornea identified as epithelial decompensation of the cornea by the investigator [MedDRA Preferred Term (PT): corneal decompensation] resolved without sequeleae. In the All Studies Cohort A total of 25 patients (4.8%) had a SAE (Table 23). Only one (0.2%) was assessed as related to IKERVIS (described above).

Laboratory findings

There was no laboratory findings reported other than those related to ciclosporin blood levels (see section 2.4.2.). In the phase IIa study, in addition to ciclosporin blood levels, creatinine and transaminases blood levels were monitored, but did not reveal any clinically significant findings.

Mean intraocular pressure (IOP) was measured in both SANSIKA and SICCANOVE at different time-points:

- At Baseline, Month 3 and Month 6 in the SICCANOVE study,
- At Baseline, Month 6, Month 12 in the SANSIKA study

IOP had also to be measured at any unscheduled visit and at the Exit visit in case of a premature discontinuation. In both studies, mean IOP of both eyes remained stable over time, and within the normal range, in both treatment groups. Only a few patients (6/741) had an IOP above the upper limit of physiological fluctuations in some occasions, i.e. 6 mmHg. But none of these patients experienced a sustained increase of IOP.

Safety in special populations

The applicant stated that for both IKERVIS and vehicle treatment groups, there is no evidence that the frequency of AE reports increased with age, sex or race. The majority of the subjects in the safety populations were aged over 65 and female. Pregnant and breast-feeding females were excluded from the study. There were no known pregnancies in the clinical studies.

IKERVIS is only intended for use in adult patients with DED and the PDCO granted a waiver for investigations in all subsets of the paediatric population. The frequency and severity of TEAEs in the elderly by age groups is summarised in Table 11.

Table 11 – Overview of TEAEs by age group (All Study Cohort)

	< 65 years	65-74 years	75-84 years	≥ 85 years	< 65 years	65-74 years	75-84 years	≥ 85 years
	n= 337	n= 121	n= 52	n= 10	n= 241	n= 97	n= 42	n= 3
	NOVA22007 (n=520)				Vehicle (n=383)			
All TAEs	200 (59.3%)	71 (58.7%)	31 (59.6%)	6 (60.0%)	115 (47.7%)	47 (48.5%)	23 (54.8%)	2 (66.7%)
Drug related TAEs	134 (39.8%)	42 (34.7%)	22 (42.3%)	6 (60.0%)	60 (24.9%)	14 (14.4%)	10 (23.8%)	1 (33.3%)
Severity of Drug related TEAEs								
Mild	37 (11.0%)	18 (14.9%)	10 (12.5%)	2 (20.0%)	26 (10.8%)	4 (4.1%)	4 (9.5%)	1 (33.3%)
Moderate	32 (9.5%)	8 (6.6%)	3 (5.8%)	2 (20.0%)	11 (4.6%)	1 (1.0%)	2 (4.8%)	-
Severe	65 (19.3%)	16 (13.2%)	9 (17.3%)	2 (20.0%)	23 (9.5%)	9 (9.3%)	4 (9.5%)	-
SAEs	11 (3.3%)	10 (8.3%)	3 (5.8%)	1 (10.0%)	10 (4.1%)	6 (6.2%)	-	-
Drug related SAEs	1 (0.3%)	-	-	-	1 (0.4%)	-	-	-
Ocular TEAEs								
Eye disorders	114 (35.7%)	30 (14.8%)	17 (18.4%)	4 (30.8%)	52 (15.2%)	14 (5.0%)	13 (12.9%)	1 (1.7%)
(General disorders and) administration site condition	111 (46.2%)	30 (13.8%)	21 (22.4%)	3 (23.1%)	13 (3.8%)	1 (0.5%)	2 (2.1%)	-
Discontinuations due to								
All TAEs	44 (13.1%)	12 (9.9%)	10 (19.2%)	2 (20.0%)	22 (9.1%)	10 (10.3%)	4 (9.5%)	-
Drug related TAEs	37 (11.0%)	9 (7.4%)	5 (9.6%)	2 (20.0%)	15 (6.2%)	6 (6.2%)	3 (7.1%)	-
Eye disorders	37 (17%)	5 (2.3%)	7 (7.5%)	3 (23.1%)	18 (3.6%)	6 (3.0%)	4 (4.3%)	-
(General disorders and) administration site conditions	27 (11.4%)	6 (2.8%)	3 (3.2%)	1 (7.7%)	5 (1.0%)	2 (1.0%)	-	-

Safety related to drug-drug interactions and other interactions

No specific studies of potential drug interactions were performed. According to the applicant, there were no data available in the scientific literature providing evidence for an interaction between ciclosporin containing ocular medicinal products and other medicines.

See also section 2.3.6. for a discussion on the potential PK/PD interactions between ciclosporin and other topical medicines.

Discontinuation due to adverse events

In total, 83 (11.2%) patients discontinued from the two phase III studies combined in the first 6 months of treatment (Double-Masked Cohort) due to an AE and 60 (8%) of these patients discontinued from the study due to a drug related TEAE. The percentage discontinuing was slightly higher for IKERVIS 0.1% than vehicle with 12.1% (48 patients) versus 10.3% (35 patients) respectively. Thirty-seven patients (9.3%) from the IKERVIS group discontinued due to a drug related AE versus 23 patients (6.8%) in the vehicle group. Most TEAEs giving rise to discontinuation were ocular AEs (instillation site pain, eye irritation, conjunctival hyperaemia).

In the All Studies Cohort (up to 12 months), 53 patients (10.2%) discontinued due to a drug related TEAEs, which were mostly ocular AEs.

Post marketing experience

There were no post-marketing data for IKERVIS at the time of this application.

2.6.1. Discussion on clinical safety

Overall, 602 persons have been exposed to IKERVIS of varying strengths, and 532 have been exposed to IKERVIS 0.1%. A total of 114 persons have been exposed to IKERVIS 0.1% for one year. The population covered by the phase II and III studies appeared to be representative of patients suffering from chronic dry eye conditions including a spread from mild to severe conditions and older age-groups. Only few patients aged 75 and older were exposed to IKERVIS including only 3 patients older than 85 years of age. Due to the limited data, no firm conclusions on the safety of IKERVIS in this older age range could be drawn. However, from the available data, there was no strong evidence for an increased risk of adverse reactions in older patients. The majority of study participants were of Caucasian origin and while the lack of data in other ethnicities was unfortunate, overall, the CHMP considered that this was not a major concern. Due to the local route of administration, the CHMP considered it unlikely that patients with hepatic or renal impairment required special considerations. As use in pregnant and breast-feeding women was not studied, use during pregnancy and in lactating women is only recommended if the benefits outweigh the risks and women of childbearing potential are recommended to use contraception. Use in pregnant or lactating women was furthermore considered missing information in the RMP and thus will be monitored post-approval. Overall, the extent of drug exposure and characteristics of the safety population were considered acceptable and sufficient to support the application for IKERVIS in the treatment of severe keratitis in adult patients with DED.

The majority of TEAEs in both the treatment and vehicle groups were ocular in nature with ocular TEAEs being more common in the IKERVIS 0.1% group compared to vehicle. Ocular TEAEs were also more severe in the IKERVIS 0.1% group compared to vehicle. Notwithstanding these higher TEAE rates in the IKERVIS 0.1% group, discontinuation rates as a result of ocular TEAEs was only slightly commoner in patients receiving IKERVIS 0.1% compared to vehicle (Double Masked Cohort).

Reporting rates of SAE were similar in the IKERVIS 0.1% and the vehicle groups, the vast majority being systemic in nature. One ocular SAE was identified in the IKERVIS 0.1% group (severe epithelial erosion of the cornea identified as epithelial decompensation of the cornea) and one in the vehicle group (severe decrease in visual acuity). While the patho-physiological mechanism that could have led to epithelial erosion of the cornea was not clear, due to the seriousness of the event, it was included in the list of adverse reactions in SmPC section 4.8 and an important potential risk was included in the RMP for post-marketing monitoring.

The most frequent TEAEs were related to the instillation of the eye drops, i.e. instillation site pain and instillation site irritation. Ciclosporin can cause ocular discomfort, which usually resolves after a short period of time. The most common adverse reactions reported as single MedDRA PT terms were instillation site pain (16%), eye irritation (9%), instillation site irritation (9%) and eye pain (4%). For the presentation in the SmPC, the CHMP considered that several related terms should be combined, e.g. eye irritation and instillation site irritation, resulting in the most common adverse reactions being eye pain (19%), eye irritation (17.8%), lacrimation (6.2%), ocular hyperaemia (5.5%) and eyelid erythema (1.7%).

Temporary blurred vision may occur due to the oil-in-water formulation, which may have a moderate influence on the ability to drive and use machines. This information was reflected in the SmPC. Furthermore, use of IKERVIS was recommended at bedtime to reduce the impact of the blurred vision.

Sustained decrease of visual acuity was only reported for few patients and to a comparable degree in the IKERVIS and the vehicle arm suggesting that ciclosporin does not increase the risk for vision loss. There was no evidence of a sustained rise in IOP above normal physiological limits in neither the IKERVIS nor the vehicle group.

There were few cases of opportunistic ocular infections, which were all reported in the two phase III studies, including one case each of bacterial keratitis and ophthalmic herpes zoster in patients receiving IKERVIS, and one case of hordeolum in the vehicle arm. All cases were moderate in severity and deemed to be possibly related to treatment. With the exception of the hordeolum case, all cases had resolved by study end. Given the immunosuppressive effect of ciclosporin, a causal relationship between the use of IKERVIS and the cases of bacterial keratitis and ophthalmic herpes zoster could not be excluded. Both events were added into the list of adverse reactions in SmPC section 4.8. Section 4.8 furthermore highlights the risk of infection in patients receiving immunosuppressive therapies such as ciclosporin and use of IKERVIS is contraindicated in patients with active or suspected ocular infection (SmPC section 4.3). As an additional effort to mitigate the risk of opportunistic infection, development and exacerbation of ocular and peri-ocular infections was included as an important potential risk in the RMP. The CHMP considered that these measures were adequate.

Ciclosporin is known to have a carcinogenic potential and the CHMP discussed the risk of ocular malignancies, in particular with a view to DED patients who might have an impaired corneal barrier, which may lead to higher intraocular levels of ciclosporin compared to healthy eyes. The applicant quoted the result of a study (Böhringer et al., 2008), showing that treatment with ciclosporin 1% or 2% over a mean duration of two years did not reveal any evidence of ocular malignancies. However, the number of eyes included in the study (76) was relatively small and not sufficient to exclude a risk of malignancy with certainty. In addition, in clinical practice, it is likely that some patients may be using ciclosporin eye drops for more than 2 years. Due to these uncertainties, peri-ocular skin cancer and conjunctival or corneal neoplasia was included in the RMP as an important potential risk. This was agreed by the CHMP although the risk was considered to be low at the doses used.

The CHMP also considered the risk of drug-drug interactions taking into account that ciclosporin interacts with efflux transporters and has been shown to inhibit some CYP and UGT enzymes (see non-clinical section for details). As there were no reports for ocular interactions, including in the scientific literature, the CHMP agreed that the risk for drug-drug interactions with IKERVIS was likely to be low (see section 2.3.6. for a detailed discussion). However, in clinical practice concomitant use of corticosteroids may occur. The CHMP therefore agreed to include a warning in the SmPC that co-administration of steroids could lead to an increased immune response.

During the development of the drug product, the formulation of IKERVIS was changed replacing the surfactant BAK (0.02% w/w) with CKC (0.005% w/w) to reduce quaternary ammonium toxicity causing ocular cell damage. However, when comparing discontinuation rates in the two phase III studies, one of which was using the BAK formulation (SICCANOVE) and the other the CKC formulation (SANSIKA), the rates were similar, suggesting that the tolerability of the two formulations was comparable.

Systemic TEAEs were less common than ocular TEAEs and the frequency was similar in both treatment groups. Few systemic TEAEs were judged to be related to treatment by the investigator. Notwithstanding the fact that data was missing for approximately 25% of subjects at the end of part 1 of the SANSIKA trial and about 30% at the end of part 2 of the trial, there was no evidence to support significant systemic absorption of ocular ciclosporin (see also section 2.4. for ciclosporin blood levels). Therefore, the CHMP considered it unlikely that any of the observed systemic adverse events was causally related to IKERVIS.

2.6.2. Conclusions on the clinical safety

Overall, the CHMP was of the view that the available safety data were sufficient to support the application for IKERVIS in the treatment of severe keratitis in adult patients with DED. The CHMP concluded that the safety

profile of IKERVIS was acceptable with the majority of adverse reactions being eye disorders and related to the instillation of the eye drops, while the risk of systemic exposure and adverse reactions was considered low. The safety profile was furthermore considered adequately reflected in the product information and all safety concerns were addressed in the RMP (see section 2.8).

The CHMP was furthermore of the view that the safety profile of IKERVIS was different from other ciclosporin products approved in the EU for systemic use, thus justifying a separate review of periodic safety update reports (PSURs) after approval. Therefore, the CHMP recommended to update the list of Union reference dates (EURD list) to include two separate entries.

2.7. Pharmacovigilance

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

Important Identified risks	None
Important potential risk	- Ocular reaction: corneal decompensation - Medication error of IKERVIS with a potential risk of local ocular infection - Off label use - Hypersensitivity (including angioedema) - Development/exacerbation of ocular/peri-ocular infection - Peri-ocular skin cancer, conjunctival or corneal neoplasia
Missing information	Use in pregnant or lactating women.

Pharmacovigilance plan

Not applicable. Only routine pharmacovigilance activities have been proposed.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
POTENTIAL RISKS		
Ocular reaction: corneal decompensation	Proposed text in section 4.8 of SmPC, with corresponding information in PIL.	None proposed
Medication error	Proposed text in section 4.2 and 6.4 of SmPC with corresponding information in the PIL.	None proposed
Off label use	Proposed text in section 4.2 of SmPC for use in children, with corresponding information in PIL. No specific other labelling language is deemed required at this time. The applicant will periodically assess whether product labelling needs to be modified.	None proposed
Hypersensitivity (including angioedema)	Proposed text in section 4.3 of SmPC with corresponding information in PIL.	None proposed
Development/exacerbation of ocular/peri-ocular infection	Proposed text in section 4.3 of SmPC with corresponding information in PIL.	None proposed
Peri-ocular skin cancer, conjunctival or corneal neoplasia	No specific labelling language is deemed required at this time. The applicant will periodically assess whether product labelling needs to be modified.	None proposed
MISSING INFORMATION		
Use in pregnancy and lactation	Proposed text in section 4.6 of SmPC with corresponding information in PIL.	None proposed

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant

show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling has been submitted by the applicant and has been found acceptable by the QRD Group.

The applicant has requested to omit the pharmaceutical form, the route of administration and the contents from the immediate labelling (single-dose container). The Group agreed that all mandatory information is not written on the primary packaging, due to its very small size, and also due to the fact that these primary packaging should be kept out of light and in a secondary packaging (which has the correct labelling)

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

A request of translation exemption of the INN on the immediate labelling (single-dose container) has been submitted by the applicant and has been found acceptable by the QRD Group.

As per the 'Compilation of QRD decisions on stylistic matters in product information' document, the QRD Group has accepted the request to use English INN on the immediate labelling because of space constraints issues.

The national language version of the INN must be used throughout the SmPC and package leaflet together with the English name in brackets after the description of the actual substance in section 2 of the SmPC and at the beginning (top introductory part) of the package leaflet.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of IKERVIS was mainly supported by two phase III trials including the pivotal SANSIKA study investigating the use of IKERVIS, 1 drop at bedtime, in 246 patients with severe DED over 6 months (vehicle controlled part 1) and 12 months (open label part 2). The patient population investigated was considered representative of the target population of adult DED patients with severe keratitis. Supportive data were available from a second phase III study SANSIKA in patients with moderate to severe DED.

Over the 6-month treatment period in SANSIKA, a global treatment effect in favour of IKERVIS over vehicle was observed regarding the change in the corneal fluorescence staining (CFS) score (0.35 units, p=0.017), which was considered to be an important secondary endpoint. Statistical significance was reached as early as Month 3 (p=0.024) and at the end of part 1 of the study (Month 6), the adjusted mean change in CFS score from Baseline was -1.76 with IKERVIS and -1.42 with vehicle (p=0.037). The difference between the two groups translated into 50% more stained dots, i.e. corneal lesions, in patients treated with vehicle compared to IKERVIS. Based on

the consultation of experts, the CHMP considered that this difference was clinically relevant, reflecting an improvement in corneal surface damage with IKERVIS that may help prevent disease progression. A beneficial effect of IKERVIS on keratitis was further supported by a non-significant trend in the pre-defined CFS responder analyses (improvement of at least 2 grades and complete corneal clearing by Month 6) in favour of IKERVIS. Post-hoc analysis showed superiority of IKERVIS compared to vehicle when using a more stringent criterion for the CFS responder rate of ≥3 grades (35.6% versus 14.5%, p = 0.001).

Furthermore, a beneficial effect on inflammation was shown for IKERVIS as indicated by the level of expression of HLA-DR, an immune-related marker elevated in conjunctival cells of DED patients. While HLA-DR expression remained elevated under vehicle, it dropped substantially with IKERVIS treatment over the course of the study. The difference between IKERVIS and vehicle was statistically significant at Month 1 (p=0.019) and Month 6 (p=0.021). While this outcome was not surprising, since HLA-DR is part of the immunomodulatory pathway of ciclosporin, it showed that indeed an anti-inflammatory effect on the ocular surface could be assumed to have been achieved. Considering that inflammation has a key role in sustaining and worsening of DED, this finding was considered of relevance, although it was an exploratory endpoint, which limits the interpretability of the finding.

Limited evidence for an improvement in tear film osmolarity was also available from a post-hoc analysis showing that in patients with an elevated osmolarity level >308 mOsms/L at Baseline, tear film osmolarity improved by Month 6 significantly more in patients treated with IKERVIS than in the vehicle group (mean change of -26.7 mOsms/L with IKERVIS compared to -16.7 mOsms/L with vehicle, p=0.048).

No relevant difference was found in any of the investigated subpopulations, including patients with Sjögren's syndrome. Globally, the treatment effects during the first 6 months of the study were either maintained or improved further during the last 6 months (12 months in total).

Uncertainty in the knowledge about the beneficial effects

The pivotal study SANSIKA failed with regard to the primary endpoint, a composite responder endpoint for both signs and symptoms of DED (CFS-OSDI composite responders with a change in CFS ≤-2 and a change of OSDI ≤-30%), mainly because of the lack of effect of IKERVIS compared to vehicle on symptoms (OSDI). IKERVIS furthermore failed to show superiority over vehicle in the majority of the other pre-defined endpoints, including OSDI, VAS, Schirmer test, use of concomitant artificial tears, investigator's global evaluation of efficacy, TBUT, lissamine green staining, quality of life score, and tear osmolarity. Broadly consistent results were seen across all efficacy endpoints in that a general improvement was observed in both treatment groups over time compared to Baseline, but the lack of a significant between-treatment effect in most of the endpoints created uncertainty as to the relevance of the treatment effect in two cases only, i.e. the change in CFS and HLA-DR expression. Experts who were consulted on this matter, suggested that ocular surface damage and inflammation (as measured by CFS and HLA-DR expression, respectively) may be factors at the beginning of a chain of relationships between all the different variables, whereby effective treatment may result in immediate improvement of these two factors, but only in a delayed response within years for all others. Such mechanism, though hypothetical, could explain the study results.

Symptoms of patients improved over the time course of the study to a similar degree in both active and vehicle groups. However, there was no significant difference between IKERVIS and vehicle neither in any symptoms score, nor with regards to use of concomitant artificial tears and quality of life. Compared to SICCANOVE, the supportive phase III study preceding SANSIKA, a considerably larger effect size was observed in SANSIKA for patients in the vehicle group (23% in SANSIKA compared to 7% in SICCANOVE). No definite reason for this difference between the two studies was found, although several possible explanations were discussed including

the heterogeneity and complexity of the disease, the change in the IKERVIS formulation and the ad libitum use of artificial tears in SANSIKA compared to the capped use allowed in SICCANOVE.

The question of the impact of the lack of effect on symptoms was referred by the CHMP to an ad-hoc expert group. The experts considered both an improvement in signs and a relief in symptoms to be important treatment objectives in DED. However, multiple factors including a potential loss in ocular surface sensitivity may influence the symptomatology in DED patients and there is no clear correlation between signs and symptoms. As a result, it has proven difficult to demonstrate an effect of a medicinal product on both signs and symptoms of DED. An improvement in signs could lead to a reduction of symptoms in the longer term, possibly after several years, but there is no evidence for such a long-term effect. Overall, the experts believed that an effect on signs alone, provided it is large enough, could be of clinical relevance, as it would help prevent disease progression resulting in potentially severe and sight-threatening complications.

Benefits of IKERVIS were also suggested in a number of post hoc analyses as well as a meta-analysis of results from SANSIKA and SICCANOVE. However, as the severe population investigated in SANSIKA was selected further to a post hoc subgroup analysis of the overall negative SICCANOVE study, the meta-analysis of the two studies would be biased in favour of IKERVIS and the CHMP considered that the best evidence of efficacy was provided by the SANSIKA data alone.

Risks

Unfavourable effects

Overall 602 persons have been exposed to IKERVIS including 114 patients receiving IKERVIS 0.1% for one year. The extent of the exposure and the demographics of the safety population were considered by the CHMP to be suitable to enable the safety evaluation of the application for IKERVIS in the treatment of severe keratitis in adult patients with DED.

The majority of adverse reactions reported were ocular in nature with the most frequently reported adverse reactions being eye pain (19%), eye irritation (17.8%), lacrimation (6.2%), ocular hyperaemia (5.5%) and eyelid erythema (1.7%). This was not unexpected for an ocular product and considering that ciclosporin was known to cause transient ocular discomfort at instillation.

Two cases of opportunistic ocular infections were reported (bacterial keratitis and ophthalmic herpes zoster) in patients receiving IKERVIS and, given the immunosuppressive effect of ciclosporin, the CHMP considered that a possible causal relationship could not be excluded. Therefore, the CHMP considered that use of IKERVIS in patients with active or suspected ocular infection should be contraindicated and that the risk of infection in patients receiving immunosuppressive therapies such as ciclosporin should be reflected in SmPC section 4.8.

No significant absorption of ciclosporin into the blood stream was observed and the frequency of systemic adverse events was similar in both the active treatment and the vehicle groups. Therefore, the CHMP considered the risk of systemic side effects to be low.

Uncertainty in the knowledge about the unfavourable effects

The safety population was generally considered representative for the proposed target population of IKERVIS. There was some uncertainty regarding the long-term safety of IKERVIS 0.1%, which could be used for several years whereas clinical safety data were only available for one year. However, overall, the CHMP considered the extend of exposure sufficient to support the application.

It was furthermore unclear whether patients aged 75 years and older and in particular those aged 85 and more were at greater risk of adverse reactions compared to other age groups, as there were too few data available in order to draw firm conclusions. However, at the same time there was no strong evidence for an increased risk in this age range. Finally, the lack of data in pregnant and lactating women was included in the RMP as missing information and will be monitored post-marketing.

There was one case of a patient experiencing epithelial decompensation of the cornea reported as corneal decompensation while using IKERVIS 0.1%. It is unclear what the underlying mechanism for this reaction could be or whether certain patients with chronic dry eye are particularly at risk of this adverse reaction. Thus, in light of the seriousness of the event, the reaction was reflected in SmPC section 4.8 and an important potential risk was included in the RMP for post-marketing monitoring.

No cases of malignancies were reported and the risk for neoplasia was overall considered by the CHMP to be low. However, due to the known carcinogenic potential of ciclosporin and since in clinical practice some patients are likely to use IKERVIS over several years, peri-ocular skin cancer, conjunctival or corneal neoplasia was included as an important potential risk in the RMP.

While there were no reports of ocular interactions between ophthalmic ciclosporin and other topically used medicines, the CHMP considered that such interactions could not be excluded given that ciclosporin is known to interact with efflux transporters and inhibit certain CYP and UGT enzymes. The CHMP welcomed the applicant's proposal for the conduct of an additional non-clinical study to explore drug-drug interactions at receptor and at the cellular level and recommended that the study be conducted post-approval. Given the totality of the available data, the CHMP considered that the risk for interaction was low. Still, concomitant use of corticosteroids may occur in clinical practice and the CHMP considered that a warning should be included in the SmPC that co-administration of steroids could lead to an increased immune response.

Benefit-risk balance

Importance of favourable and unfavourable effects

DED is a multifactorial disease that, despite different possible triggers and aetiologies, is based on a common underlying vicious circle of factors, including inflammation, which are inter-dependent and contribute to disease maintenance and progression. DED patients with severe keratitis are at risk of further complications and conventional management including artificial tear drops, gels or ointments and punctual occlusion are often not sufficient to improve the condition. Therefore, these patients represent a suitable target population most likely to benefit from ciclosporin treatment.

The available clinical evidence supported a benefit of IKERVIS on DED signs as shown by an improvement in ocular surface damage (reduced CFS). Furthermore, there was some evidence for a prolonged anti-inflammatory effect of IKERVIS (reduced HLA-DR expression), which is of relevance as inflammation is known to be key in sustaining and worsening of DED. Together, the improvements in keratitis and inflammation by IKERVIS were considered by the CHMP to be clinically meaningful even in absence of an effect on symptoms, as they help prevent disease progression and worsening.

Experts consulted during the course of the procedure considered that there was an unmet medical need for DED patients, as none of the medicines used in clinical practice to treat DED has a demonstrated effect on clinical signs and thus, many patients continue to express significant signs and suffer from impaired visual function as well as pain and irritation, requiring frequent use of artificial tears. As IKERVIS had shown a clinical relevant effect on signs, it could help address this unmet medical need.

With regards to safety, there was only one serious ocular adverse reaction associated with use of IKERVIS 0.1% and discontinuation rates due to adverse events were similar for patients receiving IKERVIS 0.1% compared to vehicle. Due to the immunosuppressive effect of IKERVIS, there is a risk of opportunistic ocular infections, but this risk was considered by the CHMP to be sufficiently mitigated by routine risk management, including a contraindication in patients with active or suspected ocular infection. Overall, IKERVIS was well tolerated with the majority of adverse reactions being eye disorders and related to the installation of the eye drops, while the risk of systemic exposure and adverse reactions was considered low.

Benefit-risk balance

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

Discussion on the benefit-risk assessment

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

In summary, the experts considered alternative explanations for the lack of effect on symptoms and suggested that there might be a lag time whereby improvement in symptoms may occur only years after improvement in signs. With regards to the clinical relevance of the observed change in corneal staining, the experts considered the results sufficiently convincing and that the observed difference between IKERVIS and vehicle represented a clinically relevant benefit. The extent of ocular surface damage was considered predictive of disease progression and thus by improving the severity of keratitis, IKERVIS may help to prevent serious complications. The effect on HLA-DR as an inflammation marker was considered by the experts to be of relevance and sufficient to assume an anti-inflammatory effect of IKERVIS at the ocular surface, which could help to disrupt the vicious disease cycle of DED. Furthermore, while use of artificial tears has been shown to help improve symptoms in DED patients, in the view of the experts there was no available treatment for DED at the time of this report with a demonstrated effect on signs.

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

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

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

Finally, the CHMP discussed the rationale for the dosing used in the phase III trials and while there were conflicting results from phase II studies, overall, the 0.1% dose strength seemed to have shown the most consistent improvements while being well tolerated. No advantage of BID dosing compared to QD dosing was expected and thus, the CHMP endorsed the dose recommendations.

4. Recommendations

Outcome

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

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being

received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

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

Not applicable.

APPENDIX

DIVERGENT POSITIONS

Divergent Position

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

The reason for the divergent opinion was as follows:

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

London, 22 January 2015

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Concepcion Prieto Yerro (Spain)	Kristina Dunder (Sweden)
……	……
Jens Heisterberg (Denmark)	Juris Pokrotnieks (Latvia)
……	……
Andrea Laslop (Austria)	Sol Ruiz (co-opted member)
……	
Karsten Bruins-Slot (Norway)	