20 July 2017
EMA/505143/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Verkazia

International non-proprietary name: ciclosporin

Procedure No. EMEA/H/C/004411/0000

Note

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

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BAK	Benzalkonium chloride
BCDVA	Best Corrected Distance Visual Acuity
BID	Twice daily
CEP	Certificate of Suitability of the EP
CFS	Corneal Fluorescence Staining
CFU	Colony Forming Units
CKC	Cetalkonium chloride
C_{max}	Maximum (plasma) concentration
CsA	Ciclosporin
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
EU	European Union
FAS	Full Analysis Set
Fpen	market penetration factor
GC	Gas Chromatography
GCP	Good Clinical Practice
HPLC	high-pressure liquid chromatography
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	Immunoglobulin
IL	Interleukin
IOP	Intraocular pressure
IR	Infrared
LDPE	Low Density Polyethylene
LLNA	Local Lymph Node Assay
LLOD	lower limit of detection
LLOQ	lower limit of quantification
LMMRM	linear mixed model for repeated measurement
LOD	Limit of Detection
LS	Least Square
MCT	Medium Chain Triglycerides
MedDRA	Medical Dictionary for Regulatory Activities

MS	mass spectrometry
PBT	persistent, bioaccumulative and toxic
$PEC_{surfacewater}$	Predicted Environmental Concentration in the surfacewater
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PK	Pharmacokinetics
PP	Per Protocol (set)
PT	Preferred Term
QID	Four times daily
RH	Relative Humidity
RMP	Risk Management Plan
RS	Randomised Set
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System organ class
SS	Safety Set
TEAE	Treatment-emergent adverse event
Th2	Type 2 T helper cell
TLC	Thin layer chromatography
ULOQ	upper limit of quantification
UV	Ultraviolet
VAS	Visual Analog Scale
VKC	Vernal keratoconjunctivitis

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Santen Oy submitted on 16 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Verkazia, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2016.

Verkazia was designated as an orphan medicinal product EU/3/06/360 on 6 April 2006 in the following condition: treatment of vernal keratoconjunctivitis.

The applicant applied for the following indication: treatment of severe vernal keratoconjunctivitis (VKC) in children and adolescents from 4 to 18 years old.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Verkazia as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

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 tests or studies.

This application is submitted as a multiple of Ikervis authorised on 19 March 2015 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0142/2015 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/0142/2015.

Information relating to orphan market exclusivity

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 because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice / Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 22 February 2007 and 19 April 2012.

The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Patrick Salmon Co-Rapporteur: Alexandre Moreau

- The application was received by the EMA on 16 December 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 10 November 2016.
- The procedure started on 20 January 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 29 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 March 2017. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 19 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at 2 clinical investigator sites in Spain and in India between 28 February 2017 to 10 March 2017. The outcome of the inspection carried out was issued on 10 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 June 2017.
- During the CHMP meeting on 20 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 27 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 June 2017 and 5 July 2017.
- During the meeting on 17-20 July 2017, 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 Verkazia on 20 July 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Vernal keratoconjunctivitis (VKC) is a rare form of ocular allergy characterised by an inflammation of the conjunctivitis with corneal involvement and tissue remodelling including papillae formation. It was first described by Arlt in 1846 who reported 3 cases of perilimbal swelling in young patients. The association with springtime (vernal) reflects the seasonal increase in signs and symptoms of the condition, particularly the high prevalence in hot, arid environments. Affected individuals have disease flares frequently during spring months, but can have signs and symptoms year round (perennially). Disease severity is defined based on clinical signs and symptoms of ocular surface inflammation. Chronic and severe forms of VKC bear an increased risk of sight threatening complications.

Verkazia is proposed for use as treatment of severe vernal keratoconjunctivitis (VKC) in children and adolescents from 4 to 18 years old.

2.1.2. Epidemiology and risk factors

VKC is a disease with great racial and geographical variation. It is most common and most severe in hot, arid environments such as the Mediterranean basin, West Africa, and the Indian subcontinent. In these areas, up to 3% of eye clinic patients present with VKC and 10% of outpatient appointments are made for signs and symptoms related to VKC. In Western Europe, VKC is less frequent. An epidemiologic survey of 6 countries in the European Union (Italy, France, the Netherlands, Norway, Finland, and Sweden) reported that while VKC can be found in both northern and southern Europe, a higher prevalence is in the southern countries (Bremond-Gignac 2008). Differences in prevalence could be due to the diversity of the gene pool, the environment (climate, socioeconomic status, and living styles), and to gene-environment interaction. Overall, the prevalence is estimated at 1 to 3 in 10,000 people in the European Union (EU).

The condition is more common in males, although this gender difference is less absolute in tropical climates. Signs and symptoms usually occur first before the age of 10 with a typical onset between 5 and 12 years of age (Leonardi 2002, Pucci 2002, Bonini 2004). The disease usually lasts 4 to 10 years and resolves after puberty, although in some cases it can continue into early adulthood. The gender discrepancy and the improvement seen during puberty have suggested a role for a hormonal influence on the disease burden.

A family history of allergic diseases occurs in around one third of VKC cases, and many patients have a history of atopy (more frequent in temperate regions) and/or other associated allergic conditions such as asthma, eczema, and rhinitis. A positive skin prick test is present in only half of the patients. Climate and geography also correlate with the associated concurrence of asthma, eczema and atopy. Limbal VKC is more often seen in patients of African or Asian descent, a racial susceptibility that appears also among those who have migrated to more temperate locations.

2.1.3. Aetiology and pathogenesis

The pathogenesis of VKC has not been completely elucidated and the aetiology may involve a variety of factors, including environmental allergens, climate, and genetic predisposition. VKC is an Immunoglobulin E (IgE) and T cell-mediated allergic reaction with additional, ill-defined, non-specific, hypersensitivity responses. Cytological, biohumoral, immunohistological and molecular biological studies indicate a key role of Type 2 T helper cells. Mast cells, eosinophils and their mediators play major roles in the clinical manifestation of VKC. In addition to typical Th2-derived cytokines, interleukins IL-4, IL-5 and IL-13, other cytokines, chemokines, growth factors and enzymes are over-expressed in the conjunctiva of VKC patients (Leonardi et al., 2009). Furthermore, structural cells, such as epithelial cells and fibroblasts, are involved both in the inflammatory process and in the tissue remodelling phase.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

VKC is differentiated from other ocular allergic conditions, such as seasonal or perennial allergic conjunctivitis, infectious conjunctivitis or ocular rosacea in children. Clinically, VKC is characterised by both conjunctival (hyperaemia, oedema, discharge) and corneal signs (superficial keratitis, corneal ulcerations, plaques, scars). Patients have a characteristic ropey, stringy mucous and/or serous discharge. Typical symptoms include photophobia, burning, pruritus, and blepharospasm. Intense ocular itching, followed by tearing and ropey, stringy mucous and/or serous discharge, and foreign body sensation are the predominant disease signs and symptoms.

VKC appears mainly seasonally but can also be perennial, chronic and/or with acute exacerbations. It usually occurs bilaterally. Unilateral cases are less frequent and more often observed at the time of disease onset.

VKC may present in three distinct phenotypes: palpebral (tarsal), limbal, and mixed forms. The hallmark sign of palpebral VKC is the presence of papillary hyperplasia of the upper tarsal conjunctiva, ranging from papillae of 1 mm of diameter to giant papillae. The tarsal conjunctiva typically develops a cobblestone appearance and, in active disease, can have mucus accumulation between the papillae. During exacerbations of palpebral VKC, punctate epithelial keratopathy may develop, which may progress to macro-erosion and sight threatening shield ulcers. Limbal VKC is characterised by the infiltration of limbal subconjunctival tissues forming nodules, sometimes accompanied by pannus of superficial neovascularisation of the peripheral cornea, making the limbus to appear thickened and opaque. They often are topped by chalky white excrescences, known as Horner–Trantas dots or Tantras dots consisting of degenerated epithelial cells and eosinophils. Limbal disease can induce stem cell deficiency that leads to compromised corneal surface, characterised by corneal vascularisation, chronic stromal inflammation, persistent epithelial defects and ingrowth of conjunctival epithelium onto the corneal surface. Palpebral forms are more prevalent in Europe and the Americas, whereas mixed and limbal forms are more seen in Asia and Africa respectively, with some geographic variation.Disease severity seems generally milder in limbal VKC compared to tarsal forms, leading some to suspect that it is the early presentation with the spectrum of the disease. At the same time, the high variability in the prevalence of certain VKC types, based on geography and atopic history, suggests that the pathogenesis of the two phenotypes may be different.

The diagnosis of VKC involves a comprehensive clinical history and ophthalmic examination and is based on the clinical symptoms of the disease as well as the findings of Trantas' dots and large cobblestone papillae that differentiate VKC from seasonal allergic conjunctivitis or perennial allergic conjunctivitis. Determination of total or specific IgE and skin test are no useful diagnostic tools being negative in 50% of patients.

A simple clinical grading system has been proposed by Bonini (2007). However, given that the clinical presentation of VKC can differ significantly depending on geographic area and genetic background, there is no consensus on the definition of severity in the scientific literature.

Table 1 Clinical grading of VKC (Bonini, 2007)

Grade	Symptoms	Conjunctival Hyperaemia	Conjunctival Secretion	Papillary reaction	Trantras dot	Corneal involvement
Grade 0 quiescent	Absent	Absent/mild	Absent	Mild to moderate	Absent	Absent
Grade1 mild intermittent	Mild and occasional	Mild	Absent/mild	Mild to moderate	Absent	Absent
Grade 2A moderate intermittent	Mild to moderate intermittent	Mild	Mild	Mild to severe	Absent	Absent
Grade 2B moderate persistent	Mild to moderate persistent	Mild to moderate	Mild to moderate	Mild to severe	Absent	Superficial punctuate keratitis
Grade 3 severe	Moderate to severe persistent	Moderate to severe	Moderate to severe	Moderate to severe with injection and swelling	Few	Superficial punctuate
Grade 4 very severe	Severe and persistent	Moderate to severe	Severe	Moderate to severe with injection and swelling	Numerous	Corneal erosion or ulceration
Grade 5 evolution	Absent or mild and occasional	Absent/mild	Absent	Mild to severe fibrosis	Absent	Absent

Generally, VKC is a benign and self-limiting condition with spontaneous resolution after puberty. However, both severe forms and chronic disease course, and sometimes unsupervised corticosteroid use (see section 2.1.5.) have been found to increase the odds for complications which can be sight threatening. Visual loss may occur due to corneal complications such as ulcers, scarring, corneal opacities, limbal stem cell deficiency, astigmatism and keratoconus.

2.1.5. Management

The management of VKC is based on a step-wise approach. The use of one and/or another treatment depends mainly on disease severity, e.g. the duration and frequency of symptoms and the severity of corneal involvement, and may vary for a given patient throughout the years.

Symptoms of itching, burning, and irritation can be managed with cool compresses and saline rinses. Preservative-free artificial tears can also be used at liberty to alleviate symptoms. These simple measures can be used irrespective of disease severity and have been reported by patients to provide significant symptomatic relief.

Among topical medications, antihistamines (levocabastine 0.05%, emedastine 0.05%) and mast cell stabilisers (sodium cromoglycate 2%-4%, lodoxamide 0.1%) are commonly used. Surprisingly, despite the major role of histamine in VKC, antihistamines alone have not proven entirely successful. Dual-acting agents with activity against H1 receptors and mast cell degranulation (olopatadine 0.1%) have been shown to be effective in the treatment of allergic conjunctivitis and are also used in cases of VKC. Topical acetylcysteine 5% to 10% has been used to reduce mucus adherence to the cornea during exacerbations. Other agents that have been tried with varying degrees of efficacy in a limited number

of studies include mitomycin-C and non-steroidal anti-inflammatory drugs (NSAIDs) including ketorolac and diclofenac.

Corticosteroids as potent anti-inflammatories and immunosuppressant are often used in moderate to severe disease with persistent symptoms and particularly to quiet disease exacerbations. However, their side-effect profile in particular with long-term use, including formation of cataracts, increase of intraocular pressure (IOP), induction and exacerbation of glaucoma, impaired wound healing, and increased susceptibility to infection including herpetic infection, is a major limitation of this treatment choice. Use of antihistamine/mast cell stabilisers as maintenance therapy and then pulse therapy with topical steroids during disease exacerbations is a common practice.

With their ability to inhibit T-cell activation, hospital-compounded preparations of 0.5% to 2% ciclosporin A (CsA) ophthalmic emulsion in olive or castor oil have been used for decades as an alternative to steroids in moderate to severe forms of VKC. Adverse reactions have been reported to be primarily limited to stinging at the time of instillation.

Finally, surgical treatment may be needed in rare cases. Surgical removal of corneal plaque is recommended only in severe, persistent cases to allow corneal re-epithelialisation. Giant papillae excision with intraoperative mitomycin-C may be considered with severe mechanical ptosis and large, coarse papillae with corneal changes.

2.1.6. About the product

Verkazia 1 mg/ml (0.1%) eye drops, emulsion is a sterile, ophthalmic emulsion that contains ciclosporin (CsA) as active ingredient. CsA 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 as well as to upregulate the release of anti-inflammatory cytokines.

Verkazia includes the same formulation as Ikervis, which has been approved via the centralised procedure by the European Commission (EC) Decision on 19 March 2015 for the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Verkazia is proposed to be used for the treatment of severe VKC in children and adolescents from 4 to 18 years old.

2.1.7. Type of Application and aspects on development

This was a complete and independent application in accordance with Article 8.3 of Directive 2001/83/EC submitted as a multiple of Ikervis in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on an unmet medical need in the absence of authorised CsA treatments for VKC in the EU and the possible irreversible sight-threatening character of the condition in particular in case of severe disease with persistent symptoms where it could be a beneficial alternative to topical steroid treatment.

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.

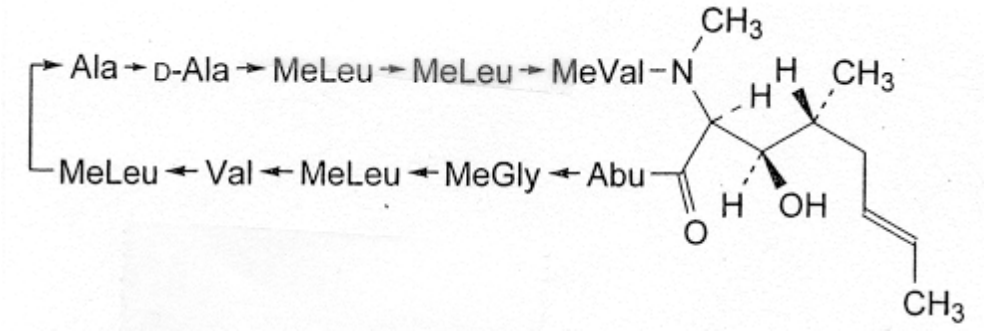
Other ingredients are: medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide and water for injections.

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[[(2S,3R,4R,6E)-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 described in the table below includes tests for appearance (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.), loss on drying (Ph. Eur.), residual solvents (GC) and microbial testing (Ph. Eur.). In addition solubility (Ph. Eur.), sulphated ash (Ph. Eur.) and bacterial endotoxins are controlled by the active substance manufacturer.

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.

Batch analysis data on 9 batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

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. Identical formulation/product was reviewed and approved as a part of a new marketing authorisation application for IKERVIS 1 mg/mL eye drops, emulsion, EU/1/15/990/001-002. IKERVIS was granted the Marketing Authorisation (MA) on 19 March 2015.

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 active substance 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.

In addition, eye drops are easy to administer and the resulting level of systemic exposure to the active 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 to 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.

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 finished 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 were 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 requirement. 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 nine 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 specifications described in the table below include appropriate tests for this kind of dosage form 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*. 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 and 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 °C / 40% RH) and under intermediate conditions (30 °C / 65% RH) for up to 36 months (pilot batches), and up to 6 months (full scale batches), as well as at accelerated conditions (40 °C/≤25%RH) for 6 months according to the ICH guidelines were provided. The batches 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 related substances analytical method is stability indicating.

In addition, one batch exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Significant drop in pH is noted in photostability studies. Hence the product is to be protected from light.

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 quality is not affected by temperature excursions that might occur during transportation.

The product was stable over the time-period of the 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 3 years shelf-life and storage conditions “Do not freeze. Store below 30°C. Keep single-dose containers in the pouch in order to protect from light and avoid evaporation” as stated in the SmPC (sections 6.3 and 6.4) 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. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

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 Verkazia was abridged and focused on the investigation of the disposition of CsA after single and repeated administration, in order to quantify the local and systemic exposure following ocular administration, and the examination of the topical effects in safety/local tolerance studies. The non-clinical development program was furthermore supplemented by reports in the scientific literature. Apart from 3 single-dose pharmacokinetic (PK) studies in rabbits and 2 mechanistic studies, all non-clinical studies were conducted in accordance with Good Laboratory Practice.

No non-clinical pharmacology studies were performed as no adequate model of VKC existed and given that CsA 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, and the pharmacodynamic effect is well described in the scientific literature both based on animal models and studies in men.

No studies in juvenile animals (PK or toxicology studies) were performed since the external parts of the eye are already fully developed in the proposed target population of children from 4 years of age and adolescents.

Furthermore, as the systemic exposure after ocular instillation of Verkazia was considered 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 CsA via other routes of administration.

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, 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 formulation, thus representing a worst case scenario in the safety assessment.

2.3.2. Pharmacology

The mechanism of action of CsA 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 VKC 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 topically administered CsA for the treatment of local immune and inflammatory disorders of the eye has been documented by means of several publications in the scientific literature for both the non-clinical and clinical setting. This includes the use for the treatment of dry eye disease/keratoconjunctivitis sicca in dogs (Kaswan et al., 1989, Olivero et al., 1991, Kaswan et al., 1994, and Gao et al., 1998). Further data showed that CsA exerts its therapeutic effect on keratoconjunctivitis sicca 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 CsA for keratoconjunctivtis sicca (Strong et al., 2005). Similar targets of the anti-inflammatory therapy with CsA in VKC, i.e. T-cell infiltration, apoptosis, and cytokines, have been postulated also for allergic inflammation of the eye surface such as VKC. Furthermore, the efficacy and safety of CsA in VKC patients has already been investigated and discussed in the literature (Gupta 2001, Pucci 2002, Pucci 2010, Tesse 2010, Labcharoenwongs 2012, Leonardi 2013, and Yucel 2015).

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 Verkazia (see summary of systemic absorption of CsA after ocular administration in the following sections), no safety pharmacology studies were conducted. This was considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

The goal of the non-clinical PK programme was to characterise the ocular bio-disposition of CsA following single and multiple ocular administrations of Verkazia, and to compare it with Restasis (0.05%), which is authorised in the United States of America for the treatment of KCS and was used as a reference product because it was the only other CsA-containing eye drop formulation available for human use at the time of the non-clinical development. To this end, the applicant performed single and multiple dose studies in rabbits.

Validated high-pressure liquid chromatography (HPLC) mass spectrometry (MS), ultra-performance liquid chromatography-MS/MS and liquid chromatography-MS/MS methods were used for the determination of CsA concentrations in rabbit whole blood and various ocular tissues (cornea, conjunctivae). 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 proposed for commercial use. Furthermore, the old formulation included vitamin E (dl-α-tocopherol), 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 dl-α-tocopherol 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

CsA concentrations increased in a dose proportional manner in the cornea and conjunctiva after both single and multiple instillation of 50 µl of 0.25, 0.5 and 1 mg/ml CsA eye drops and displayed half-lives of 3.19-6.68 hours and 26.21-53.25 hours in the conjunctiva and cornea, respectively. Maximum concentration (c_{max}) was attained generally at 0.33 hours. No (conjunctiva) or slight (cornea) accumulation of CsA in ocular tissues was observed following multiple administrations. CsA AUC levels in the cornea were found to be doubled after a single instillation of CsA eye drops (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 10 days) of CsA 0.1% once daily, tissue CsA concentrations (c_{min}) were observed in the cornea at steady state similar to those observed following a 10-day treatment with Restasis (0.05%) twice daily (BID).

- Systemic exposure

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

Distribution and metabolism

Radioactivity levels were measured in ocular (including cornea and conjunctiva) and non-ocular tissues of rabbits treated with ^{3}H-CsA formulations (both Verkazia and Restasis) for 7 days, at 1 hour and 24 hours after the last administration. No significant difference was found between both formulations. 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 CsA metabolites considering that the higher count levels were found in the major elimination organs, liver and kidney.

Another study was performed to investigate CsA penetration in the cornea and conjunctiva of pigmented rabbits after 4 daily (QID) 20 µl instillations over 10 days of Verkazia (CsA 0.1% cationic emulsion) compared to an oily 1% CsA solution. This study suggested that the cationic emulsion of Verkazia has a slower penetration compared to the oil solution (although penetration lasted longer due to the longer residence time of the cationic vehicle on the ocular surface) and avoids successive peaks and lows following each instillation due to a slower rate of elimination.

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). This was considered acceptable.

2.3.4. Toxicology

Single and repeat dose toxicity

The applicant did not perform any single or repeat dose toxicity studies due to the low systemic exposure after ocular use of Verkazia. However, repeated doses of Verkazia were tested in rabbits to investigate local tolerance (see below).

The applicant furthermore provided literature data including both non-clinical and clinical long term use (up to 3 years) of eye drops containing CsA. This included a 6-months study in dogs being treated with

veterinary oil-based CsA-containing ointment (0.2%), showing that BID administration was well tolerated with no safety concerns, either locally or at the systemic level.

Genotoxicity, carcinogenicity and reproduction toxicity

As the systemic exposure after ocular instillation of Verkazia was negligible, the applicant did not perform genotoxicity, carcinogenicity or reproductive and developmental toxicity studies, and instead summarised relevant information from the scientific literature. This approach was considered acceptable.

CsA is referred to in the literature as a non-genotoxic human carcinogen (McClain 2001, Hernandez 2009). The carcinogenic potential has been previously investigated (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 CsA 1 mg/ml, even in eye tissues.

No adequate and well-controlled studies in pregnant or breast-feeding women were available with either oral CsA or ophthalmic dosage forms, however Ryffel (1983) reported no teratogenic effects of CsA in rats and rabbits up to maternal toxic doses of 30mg/kg, but there was some evidence for reproductive toxicity at high (>maternal toxic) doses, at which foetal death and growth retardation of the off-spring occurred.

Local tolerance

Local tolerance was investigated in four 28-day studies in rabbits with instillations in the eyes four times a day in line with the Note for Guidance on non-clinical local tolerance testing on medicinal products (CPMP/SWP/2145/00). Two of these studies used a CsA formulation with BAK and two used the CKC formulation.

Briefly, 0.25, 0.5 and 1 mg/ml CsA eye drops were well tolerated in rabbits receiving multiple daily instillations (50 µL) at 4-hour and 90-minute intervals for 28 days. 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 at a concentration of 1 mg/ml but no histopathological findings were reported. Moreover, slight transient conjunctivae irritation reactions accompanied with slight focal unilateral and chronic conjunctivitis on the bulbar conjunctiva histopathology findings were also noted in a study with CsA 0.1% 0.005% w/w CKC. However, these findings were also seen in an untreated eye and were considered attributable to the daily repeated instillations. The minor epithelial ulcerations or linear marks of the cornea also seen in this study were considered attributable to slight traumatisms and not treatment related.

Removal of dl-α-tocopherol had no impact on the ocular tolerance of the formulation and the change of the excipient from 0.02% w/w BAK to 0.005% w/w CKC did not elicit any ocular intolerance and was considered safe and well tolerated.

Corneal sensitivity following repeated instillation was examined in a study with rabbits. Verkazia (CsA 0.1%) 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 as well as a murine UV-LLNA assay and a study in guinea pigs to assess the phototoxic and photoallergic potential. The LLNA assay showed that neither the BAK nor

CKC containing formulations induced delayed contact hypersensitivity. Furthermore, Verkazia was devoid of phototoxic and photoallergic potentials.

The applicant also presented the results of three non-GLP studies examining different safety attributes of the cationic emulsion in rabbits. In the first of the three studies (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 CsA 0.5 mg/ml containing 0.005% CKC was well tolerated and was comparable to other BAK free CsA 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 0.005% w/w CKC 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.

The absence of studies in juvenile animals was considered acceptable given that the systemic exposure after ocular instillation of Verkazia was negligible and considering that the external parts of the eye are fully developed in the target population.

2.3.5. Ecotoxicity / environmental risk assessment

CsA is not considered to be an endocrine disrupting compound (Daughton 2001). Furthermore, CsA is not a persistent, bioaccumulative and toxic (PBT) substance as the octanol/water partition coefficient (log Kow) does not exceed 4.5.

Using the default value for the market penetration factor (F_{pen}) of 1% and assuming a maximum dose of 4 drops of CsA 0.1% per eye and day, the predicted environmental concentration in the surfacewater ($PEC_{surfacewater}$) of CsA was calculated to be 0.001 µg/L, which is below the action limit of 0.01 µg/L. The applicant furthermore reflected on the fact that CsA is already used in existing marketed products used for the prevention of transplant organ rejection, and for the treatment of psoriasis, severe rheumatoid arthritis and ulcerative colitis. No significant increase in environmental exposure is anticipated given the rarity of VKC and the low topical doses required for treatment.

Therefore Verkazia is not expected to pose a risk to the environment.

Table 2 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**
$PEC_{surfacewater}$	0.001	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 for VKC were not available at the time of this report. Furthermore, the pharmacodynamic effects of CsA are well described in the scientific literature and the safety and efficacy of ophthalmic preparations of CsA has already been investigated in the clinical setting. Therefore, 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 CsA after ocular treatment with Verkazia (see also PK discussion below).

Pharmacokinetics

The exchange of BAK for CKC and removal of vitamin E in the final Verkazia 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 CsA 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 Verkazia 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 CsA metabolites. The CHMP considered this explanation difficult to follow given that data in the scientific literature suggest that CsA is not metabolised in the eye (at least in dogs and rabbits; Acheampong 1999, Wiederholt 1986), which was also the reason why no drug metabolism studies were conducted in support of this application. Overall, as CsA is a well-known active substance, the significance of this finding was considered limited.

The CHMP also accepted that no *in-vitro* or *in-vivo* drug interaction and metabolism studies were carried out. While, CsA is known to be a strong inhibitor of several transporters such as P-glycoprotein, breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) and organic anion-transporting polypeptide B1, only transporters of the MRP family and BCRP are expressed and functional in human cornea. The clinical relevance of CsA's possible interference with these efflux transporters within the eye was not entirely clear at the time of this report. To avoid absorption interference and partial wash out of the product due to the excess instilled volume, the SmPC recommends that Verkazia should not be administered at the same time with other eye drops, but rather 15 minutes apart, which was considered adequate by the CHMP. Furthermore, the applicant is already conducting a drug-drug interaction study as recommended by the CHMP to be conducted after

the approval of Ikervis for the treatment of dry eye disease. The study aims at obtaining additional information on the interaction potential at the transporter level (two year study program), as well as at the cellular level (one year study program). The applicant should consider the impact of the study results, once available, for Verkazia including the need for an update of the product information.

Toxicology

Systemic exposure to CsA after ocular use was found to be negligible and thus the risk of systemic side effects due to circulating CsA 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 CsA 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 (see also discussion on clinical safety in section 2.6.1.). Furthermore, evidence for reproductive toxicity at high systemic doses has been observed in rats and rabbits. Therefore, despite the low systemic exposure at therapeutic doses and absence of any adverse pregnancy outcome having been observed in the clinical setting (see also section 2.6.), Verkazia is not recommended in women of childbearing potential not using effective contraception and use during pregnancy and in lactating women is only recommended if the benefits outweigh the risks. Use in pregnant or lactating women is furthermore considered missing information in the RMP and will be monitored post-approval.

No overt adverse effects attributable to Verkazia were identified in the local tolerance toxicity studies, nor in the other toxicology studies conducted. 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 VKC is a chronic disease requiring regular administration of Verkazia over prolonged periods of time, 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. Furthermore, a 6 months study has previously been performed in dogs with a veterinary 0.2% CsA ointment showing that BID application was well tolerated with no safety concerns, either locally or at the systemic level.

The absence of studies in juvenile animals was considered acceptable given that the systemic exposure after ocular instillation of Verkazia was negligible and considering that the external parts of the eye are fully developed in the proposed target population which includes children from 4 years of age and adolescents.

2.3.7. Conclusion on the non-clinical aspects

Overall, the CHMP was of the view that the non-clinical data were sufficient to support the application for a marketing authorisation of Verkazia in the treatment of severe VKC in children from 4 years of age and adolescents. The CHMP furthermore concluded that Verkazia was not expected to pose a risk to the environment

2.4. Clinical aspects

2.4.1. Introduction

Good Clinical Practice (GCP)

The applicant confirmed that the clinical trials were performed in accordance with GCP.

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.

Table 3 Tabular overview of clinical studies

Study name (Number)	No of randomised patients	Dose of NOVA22007 Comparator Duration of treatment	Primary objective
Phase II/III study providing design information for Phase III			
Phase II/III study NOVATIVE (NVG05L101)	118 Patients with VKC	**Period I:** NOVA22007 0.05% NOVA22007 0.1% Vehicle One drop QID 1 month **Period II:** 3 month safety follow up NOVA22007 0.05% NOVA22007 0.1% One drop QID	Dose finding, to test the hypothesis that NOVA2207 is superior to its vehicle
Phase III pivotal study			
Phase III VEKTIS (NVG09B113)	169 Patients with severe VKC	**Period I:** NOVA22007 0.1% QID or NOVA22007 BID Vehicle One drop QID 4 months **Period II:** 8 month safety follow up NOVA22007 0.1% QID or NOVA22007 BID One drop QID	To compare the efficacy of NOVA 22007 to its vehicle, identify the most appropriate dose and assess long-term safety of NOVA22007 over a 12 month period

Furthermore, the applicant presented the reports of 4 clinical trials (2 Phase II and 2 Phase III studies) which investigated CsA 0.1% eye drops in patients with dry eye disease:

- Phase IIa (N09F0502) in 53 Sjögren patients with moderate to severe dry eye disease;
- Phase IIb ORA (NVG08B112) in 132 patients with mild to moderate dry eye disease;
- Phase III SICCANOVE (NVG06C103) in 495 patients with moderate to severe dry eye disease;
- Phase III SANSIKA (NVG10E117) in 246 patients with severe dry eye disease.

The data from these studies were considered supportive in particular with a view to the safety evaluation (see section 2.6.).

2.4.2. Pharmacokinetics

Due to the ophthalmic route of administration and the local site of action, no specific clinical PK or metabolism studies were conducted in support of this application. However, in order to evaluate a possible systemic exposure to Verkazia, blood samples were collected in patients included in the Phase II/III NOVATIVE study and in the Phase III VEKTIS study (see sections 2.5.2. and 2.5.3. for a description of the study designs and main results)

In VEKTIS ciclosporinaemia was measured using a specific HPLC-MS assay. The quantification method used was a validated bioanalytical method with a lower limit of quantification (LLOQ) of 0.1 ng/mL, a low limit of detection (LLOD) of 0.05 ng/mL, and an upper limit of quantification of 5 ng/mL. The other method used in the NOVATIVE study was an HPLC-MS assay with a LLOQ of 2 ng/mL.

In NOVATIVE, a blood sample was collected at selected centres before morning instillation of the investigational medicinal product at the Week 4 (Month1) visit. CsA blood levels were detectable in very few treated patients: 1/10 patients treated with CsA 0.05% QID (CsA blood level of 0.13 ng/mL) and 4/6 patients treated with CsA 0.1% QID. The highest detectable CsA blood level was 0.33 ng/ml in 1 patient treated with CsA 0.1% QID.

In the VEKTIS study, blood samples for CsA levels were taken from 166 patients at baseline, Month 2, Month 4 and Month 12. CsA concentration data were summarised by visit using frequency distribution of values below the lower limit of detection and values at least equal to the LLOQ.

For most of the VEKTIS patients (33/50 in the high dose group, and 41/47 in the low dose group), after 4-month treatment no (<LLOD) or negligible (<LLOQ) systemic exposure to CsA was detected. Some patients showed quantifiable CsA at the same time point: 14/48 (29.2%) in the high dose group and 5/41 (12.2%) in the low dose group, with some values as high as 0.670 ng/ml in the high dose group and 0.336 ng/ml in the low dose group showing that systemic absorption of CsA did occur (LLOQ = 0.10 ng/ml) although to a greater extent in the high dose group. The same pattern was observed when analysing the data separately for children and adolescents (4-11 years; and >11 years) showing a systemic passage of CsA in some patients and more specifically for those receiving the high dose.

At Month 12, there was still a number of patients (12/68 in the high dose group vs. 5/61 in the low dose group) with quantifiable CsA in the blood, although to a lesser extent when compared to Month 4, suggesting that there is no accumulation with chronic administration even if a limited systemic passage exists. Measurable values up to a maximum of 0.291 ng/mL and 0.300 ng/mL for the high and the low dose group, respectively, were observed.

2.4.3. Pharmacodynamics

No specific pharmacodynamic studies were conducted with Verkazia since an adequate model of VKC did not exist and in light of the ophthalmic route of administration as well as the local site of action. Furthermore, CsA is a well-known active substance for which the mechanism of the immunosuppressive and anti-inflammatory actions has been well-described in the scientific literature.

In patients with VKC, CsA, following ocular administration, is passively absorbed into T-lymphocyte infiltrates in the cornea and conjunctiva where its binding to cyclophilin A inactivates calcineurin phosphatase. CsA-induced inactivation of calcineurin inhibits the de-phosphorylation of the transcription factor NF-AT (nuclear factor of activated T-cells) and prevents NF-AT translocation into the nucleus, thus blocking the release of pro-inflammatory cytokines such as interleukin-2 (as well as of other cytokines) and subsequent T-lymphocytes activation. Blocking NF-AT further interferes in the allergic process.

CsA is also known to inhibit histamine release from mast cells and basophils through a reduction in IL-5 production, and may reduce eosinophil recruitment and effects on the conjunctiva and cornea. It furthermore up-regulates the release of anti-inflammatory cytokines. All available evidence suggests that CsA acts specifically and reversibly on lymphocytes. It does not depress haemopoiesis and has no effect on the function of phagocytic cells.

2.4.4. Discussion on clinical pharmacology

Given that there was no adequate model of VKC and since Verkazia is used locally whereby there was no evidence of significant systemic absorption (see below), the CHMP considered it acceptable that no specific clinical pharmacology studies were conducted in support of this application. The CHMP also took into account that CsA is a well-known immunosuppressant and anti-inflammatory agent which's

mechanism of action has been extensively documented in the scientific literature.

Ciclosporinaemia occurred in nearly 30% of the patients receiving CsA 0.1% QID. Quantifiable levels were found in 29.2% of the high dose group, and in 12.2% of the low dose group by Month 4, with some values as high as 0.670 ng/ml in the high dose group and 0.336ng/ml in the low dose group. Overall, systemic exposure was considered negligible as the observed blood levels were substantially lower compared to systemic CsA used for prevention of graft rejection (e.g. c_{max} of 750-1000 ng/ml in paediatric renal transplant recipients [Wigger 2003; Rodriguez 2005]). Notably, ciclosporinaemia was still present at Month 12 although to a lesser extent when compared to Month 4, suggesting that there was no accumulation with chronic administration even if a limited systemic passage through the nasal mucosa as a result of the eye drops being cleared from the ocular surface through the lachrymal draining system occurred. This information had been adequately reflected in SmPC section 5.2.

2.4.5. Conclusions on clinical pharmacology

In light of the local route of administration of Verkazia and since no significant systemic exposure occurred, the CHMP considered that the lack of specific pharmacodynamics or pharmacokinetic studies was acceptable. Available data from the scientific literature and blood samples collected during the clinical trials program were considered sufficient in order to support the application for Verkazia in the treatment of severe VKC in children from 4 years of age and adolescents form a clinical pharmacology point of view.

2.5. Clinical efficacy

The clinical programme for Verkazia included 2 Phase 3 studies: the confirmatory pivotal Phase 3 VEKTIS study (NVG09B113) performed in severe VKC patients and the supportive Phase 2/3 NOVATIVE study (NVG05L101) in moderate to severe VKC.

2.5.1. Dose response study(ies)

According to the applicant, the chosen dose regimen in NOVATIVE (one eye drop four times daily [QID] of CsA 0.05% and 0.1%) was derived from the literature, multiple reports and current medical practices using off-label, hospital-made topical CsA.

The dose regimen of one eye drop QID and twice daily (BID) of CsA 0.1% investigated in VEKTIS was selected based on preclinical data, on results of previously conducted studies and on clinical practice. In the clinical studies published up to now, CsA up to 2% (in castor or olive oil) administered 4 times daily up to 6 months has shown efficacy on both signs and symptoms of VKC. At the same time, while no dose response relationship can be derived from the available non-clinical data, long corneal elimination half-life (26.21-53.25h) in rabbits suggests the need of less frequent instillations, e.g. BID. In addition, 4 times daily administration might be difficult in practice, e.g. for children if attending school despite disease severity, and might be associated with greater systemic and local safety concerns. Finally, results of post-hoc analyses of NOVATIVE in patients with active VKC with severe keratitis suggested the potential for a greater benefit of the 0.1% CsA dose over the 0.05% dose. Therefore, it was decided to test CsA 0.1 % BID and to compare it to 0.1 % QID in VEKTIS.

2.5.2. Main study

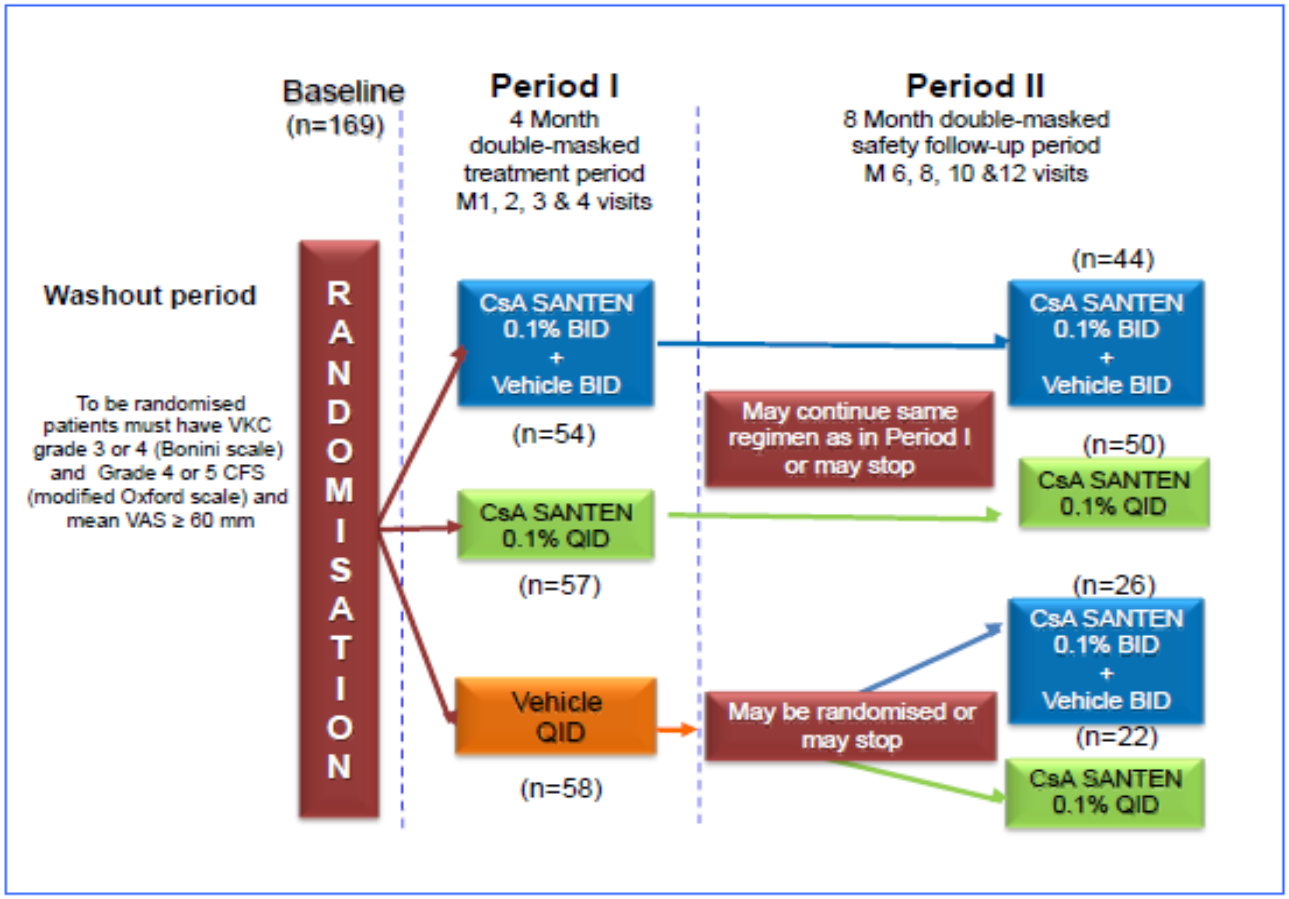
VEKTIS (NVG09B113): Multicenter, randomized, double-masked, 3 parallel arms, placebo controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL

(ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis

Methods

The study was divided in 2 parts: a 4-month efficacy evaluation treatment period and an 8-month safety follow-up period. Both study periods tested NOVA22007 (CsA 1 mg/mL) administered 2 or 4 times daily in children or adolescents with severe VKC. The first 4-month randomized, double masked study treatment period was designed as a superiority study using vehicle emulsion as control. During the subsequent 8-month safety follow-up period, patients were allowed to continue on 1 of the 2 active regimens. Patients enrolled early in the study for whom the VKC allergy season was ongoing at the end of the 4-month efficacy evaluation period and patients who did still presented signs and symptoms of VKC according to the investigator judgment were allowed to continue on study treatment. Also, patients who experienced a recurrence of active VKC or a worsening in VKC symptoms following the discontinuation of study treatment outside of the VKC allergy season during the remaining months of their 8-month safety follow-up period were allowed to resume treatment with NOVA22007 in a masked fashion according to the investigator judgment.

Figure 1 – Design of VEKTIS



Study Participants

Patients who met the following main **inclusion criteria** were eligible to enrol in the study:

- Male or female patients from 4 to less than 18 years of age.
- Female of childbearing potential had to have a negative pregnancy test plus a medically

acceptable, highly effective method of birth control.

- History of at least 1 recurrence of VKC in the past year prior to enrolment.
- Patients not receiving any treatment for an established and active VKC; or patients already receiving treatment for their VKC provided treatment was stopped according to the wash-out period specified in the exclusion criteria.
- Active severe VKC consistent with grade 3 or 4 of Bonini scale (Bonini 2007) with severe keratitis (grade 4 or 5 on the modified Oxford scale).
- Mean score of 4 subjective symptoms (photophobia, tearing, itching and mucous discharge) ≥ 60 mm using a 100 mm VAS (where "0" means no symptom and "100" means the worst that had been ever experienced).
- Patient enrolment had to occur early during the site VKC season in order to allow the 4-month treatment period during the site VKC season

Patients who met the following main **exclusion criteria** were not allowed to enter the study:

Ocular Conditions/Diseases

- Any relevant ocular anomaly other than VKC interfering with the ocular surface including trauma, post radiation keratitis, severe blepharitis, rosacea, corneal ulcer, etc.
- Abnormal lid anatomy, abnormalities of the nasolacrimal drainage system or blinking function in either eye.
- Active herpes keratitis or history of ocular herpes.
- History of ocular varicella-zoster or vaccinia virus infection.
- Active ocular infection (viral, bacterial, fungal, protozoal).
- Any ocular diseases other than VKC requiring topical ocular treatment during the course of the study.
- Contact lenses wear during the study.

Ocular Treatments

- Topical and/or systemic use of corticosteroids within 1 week prior to enrolment.
- Topical CsA, tacrolimus or sirolimus within 90 days prior to enrolment.
- Scraping of the vernal plaque within 1 month prior to the Baseline visit.
- Ocular surgery within 6 months prior to the Baseline visit (excluding surgical treatment of the vernal plaque).

Systemic Conditions/Diseases or Treatments

- Disease not stabilized within 30 days before the Baseline 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 systemic immunosuppressant drugs within 90 days before the Baseline Visit.
- Known hypersensitivity to one of the components of the study or procedural medications, history of malignancy in the last 5 years, or pregnancy or lactation at the Baseline Visit.

Treatments

Patients were instructed to instil 1 drop of study treatment into the lower conjunctival sac of each eye 4 times daily: in the morning, at noon, in the afternoon and in the evening (with approximately 4 hours between each instillation) and to reduce the systemic absorption a nasolacrimal occlusion compression of lacrimal ducts had to be applied. Study medication was provided in single-unit container yielding 2 drops of study medication (1 drop for instillation in each eye). Patients in the BID treatment arm received active treatment in the morning and evening and vehicle at noon and in the afternoon.

The formulation of the vehicle control was exactly the same formulation as NOVA22007 but excluded the active substance.

Patients involved in VEKTIS were allowed to use unpreserved tear substitutes up to 4 times a day only in case of worsening of the VKC symptoms and inability to have a visit for rescue corticosteroid therapy prescription.

Rescue Therapy

Rescue treatment consisted of dexamethasone 0.1% eye drops provided by the sponsor, 1 drop 4 times daily for 5 days. A maximum of 2 courses of rescue between 2 scheduled visits during the 4-month treatment period and a maximum of 4 courses of rescue between 2 scheduled visits during the follow-up period were allowed.

The need for rescue medication was assessed by the investigator during a visit (or phone call for a second course) and rescue medication was given if the patient satisfied the following conditions:

- Keratitis worsening of at least one grade on the modified Oxford scale or maintained during 2 months at the entry level, and/or
- Symptom worsening of at least 1 centimetre on at least 1 of the 4 symptoms along with the worsening of the mean of the 4 symptoms or maintenance at the entry level.

Patients receiving rescue medication had their intraocular pressure assessed at each study visit as for any patient and were carefully monitored because of the risks of glaucoma as well as the occurrence of adverse events (AEs) with an increased risk of infections.

Objectives

The primary objective of the study was to compare the efficacy of 2 different dosing regimens of NOVA22007 versus vehicle on both the evolution of severe keratitis and the need for rescue medication.

The secondary objectives were to assess the safety and tolerability including ocular tolerance of 2 dosing regimens of NOVA22007 versus vehicle and to assess the efficacy of 2 dosing regimens of NOVA22007versus vehicle on other signs and symptoms of VKC not covered in the primary objective.

Outcomes/endpoints

The primary efficacy endpoint was the penalty adjusted CFS score at 4 months, defined as the mean of the 4 efficacy scores taken at each monthly visit, based on:

- Keratitis assessed by corneal fluorescein staining (CFS) using the modified Oxford scale [7-point ordinal scale (0, 0.5, and 1 to 5)].
- Need for rescue medication.

- Occurrence of corneal ulceration.

The efficacy score was calculated as follows:

Patient's score at month X = CFS (Baseline) – CFS (Month X) + penalty(ies).

Penalty for rescue medication: -1 (per course, with a maximum of 2 courses between 2 scheduled visits).

Penalty for corneal ulceration: -1 (per occurrence).

Secondary Efficacy Endpoints

- CFS score assessed with the modified Oxford scale at Baseline, Month 1, 2, 3 and 4.
- Use of rescue therapy at Month 1, 2, 3, and 4.
- Occurrence of ulcer Month 1, 2, 3 and 4.

Other Efficacy Endpoints

- Visual Analog Scale (VAS) score at Month 1, 2, 3 and 4. The 4 main symptoms (photophobia, tearing, itching and mucous discharge) assessed using a 100 mm VAS, individually and globally (average of the 4 measures) at each visit during the 4- month efficacy evaluation treatment period.
- CFS Responder rate at Month 2, 3 and 4. A responder was defined as a patient (1) with a CFS score at Month 4 equal or smaller than 50% of the baseline CFS, (2) who did not withdraw from the study for a reason possibly due to treatment, (3) free from occurrence of ulceration and (4) free from use of rescue medication in the last 3 months of treatment.
- Artificial tears use at Month 1, 2, 3 and 4.
- Quick questionnaire at Month 1, 2, 3 and 4 (as well as Month 12).

  The QUICK questionnaire is a simple instrument, which was developed to measure health-related quality of life (HRQoL) in children with VKC (Sacchetti 2007). It contains 16 items allocated into 2 domains: symptoms (12 items) and impact of VKC on daily activities (4 items). Each item which relates to what the patient experienced in the past 2 weeks, is scored according to a 3 point scale where 1=never, 2=sometimes and 3=always. QUICK scores range from 0 to 100, the highest score indicating worse HRQoL.
- Investigator Global Evaluation of Efficacy at Month 4 using the following rating scale: 3 = Very satisfactory, 2 = Satisfactory, 1 = Not very satisfactory, and 0 = Unsatisfactory.

Furthermore, because some patients continued active study medication during the 8-month follow-up period and although not vehicle controlled, some exploratory efficacy assessments were performed during this period.

Sample size

Assuming a 1.25 grade difference in primary endpoints between active group and vehicle control and a standard deviation of 2 based on observations in the NOVATIVE study, and setting the two-sided alpha risk at 2.5% to take into account a multiplicity adjustment for the 2 tested dose regimens, a sample size of 50 patients per group was required to have 80% chance (power) and to show a significant difference between the most efficacious dose and vehicle. A provision of 12% was arbitrarily added to the sample size (56 patients per group) for the decrease of power linked to an early end of VKC season in some regions and possibly early withdrawals.

Randomisation

A 1:1:1 allocation ratio based on a (centralised) computerized randomization scheme was used for the treatment assignment. Patients enrolling into the 8-month treatment follow-up period and initially assigned to vehicle, were switched to one of the two active study treatment arms in a 1:1 ratio.

Blinding (masking)

This was a double-masked study. Masking was achieved by providing the study medication (NOVA22007 and vehicle) in identical masked treatment units and by identifying each study medication by a treatment number. Investigators were allowed to unmask a patient in emergency cases only (e.g. serious adverse event). The Data Safety Monitoring Board remained masked throughout the study.

Statistical methods

The following analysis populations were considered:

The Safety Set (SS) consisted of all patients randomized in the study for whom there was any evidence that they used study medication and for whom any follow-up information was available.

The Full Analysis Set (FAS) consisted of randomized patients, potentially excluding few patients corresponding to the failure to take at least 1 dose of study medication and very early withdrawal (first week after randomization) definitely not related to study medication and leading to the lack of any post randomization data.

The Per Protocol set (PPS) excluded FAS patients with any major protocol deviations that may have impacted the efficacy analysis.

The main efficacy population was the FAS.

Descriptive statistics are presented per treatment group. Mean, standard deviation, minimum, median, maximum and number of observations were used for quantitative variables, and frequencies and percentages for categorical variables. Regarding the efficacy variables concerning both eyes, descriptive statistics and statistical analyses were only done for the worst eye at inclusion. Safety variables recorded in both eyes were analysed for both the worst eye and the other eye separately. The worst eye was defined as the eligible eye with the highest Oxford score for corneal staining at Baseline. In case both eyes had the same score at Baseline the right eye was considered.

Primary Analysis of the Primary Efficacy Endpoint

Superiority of each dosing regimen of NOVA22007 compared to vehicle was tested using a linear model (analysis of covariance [ANCOVA]) with 2 covariates: the treatment and the proportion of time spent in being exposed to the randomized treatment within the VKC season. The model was applied separately to the CFS, the rescue medication and ulcer components of the composite endpoint.

The type I error was adjusted through the Hochberg's procedure for comparing each dose versus vehicle. The procedure started with the largest p value compared to 0.05 followed by the smallest p-value compared to 0.025 if the largest p-value was not significant (ascending procedure).

The robustness of the primary result (on the FAS) was assessed using the PP population and the set of all randomized patients (sensu stricto). Another sensitivity analysis was based on the FAS and observed cases without any imputation of missing data (mean per month of available data).

Secondary Analyses of the Primary Endpoint:

A secondary analysis of the primary endpoint was performed using a repeated measures analysis of variance (general linear mixed model) in order to estimate the magnitude of the treatment effect at each month.

Other Secondary Efficacy Analysis:

The change from Baseline in the modified Oxford scale value as well as in each symptom (photophobia, tearing, itching and mucous discharge assessed using a 100 mm VAS) was fitted by a general linear mixed model for repeated measurements (LMMRM).

The rate of responders was compared with a logistic regression using the treatment and the proportion of time spent under treatment during the VKC season as covariates.

The frequency distribution of the number of courses of rescue medication for each group was provided and each dose was compared to vehicle through a non-parametric Savage test.

The QUICK questionnaire was analysed by a general LMMRM. The 2 domains of the scale (the Symptoms domain and the Daily Activities domain) were analysed separately.

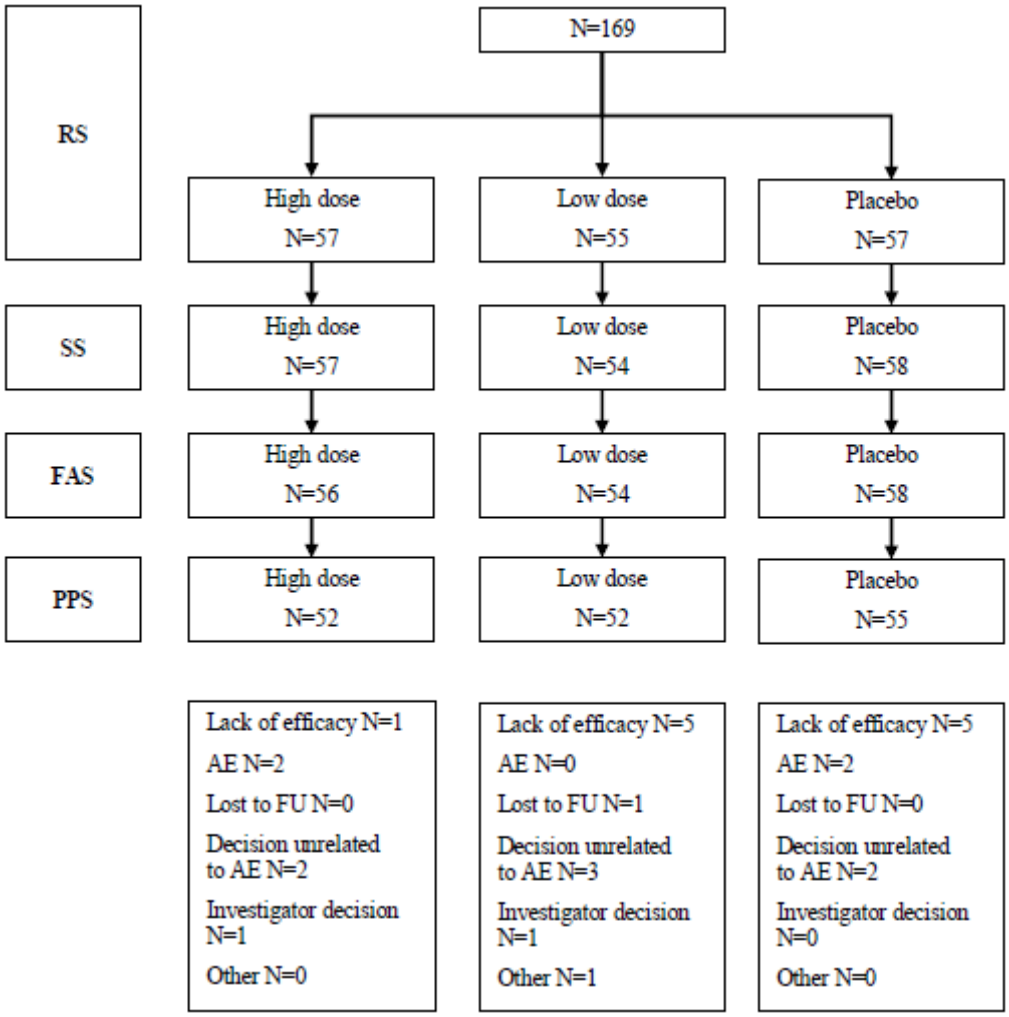
Results

Participant flow

A total of 169 patients were randomized into the study. These patients were recruited in 11 countries and a total of 101 patients were included in Europe.

Overall, 26 patients (15.4%) withdrew from the study. The most frequent primary reasons for withdrawal were lack of efficacy in 11 patients (6.5%) and patient decision unrelated to an AE in 7 patients (4.1%). For both, the low dose group (n=5 [9.3%]) and the vehicle group (n=5 [8.6%]), more patients withdrew due to lack of efficacy compared to the high dose group (n=1 [1.8%]).

Figure 2 – Patient Disposition (VEKTIS, 4-Months Randomised Period)



Recruitment

Date of First Patient Enrolled: 29 Apr 2013.

Date of Last Patient Completed: 01 Feb 2016.

Conduct of the study

The study protocol was amended twice. Only the second amendment was after recruitment of the first patient. It was a country specific amendment for Croatia to reflect national requirements for contraception. The statistical analysis plan was also changed including the addition of the randomised set (RS) for sensitivity analyses of the primary endpoint, addition of a Follow-up Total Set for the 8-month follow-up analyses.

Baseline data

The FAS comprised 127 children (75.6%) and 41 adolescents (24.4%). Mean age was 9.2 years (standard deviation [SD]: 3.3). There were more male (n=132 [78.6%]) than female patients (n=36

[21.4%]) and the majority was of Caucasian origin (n=119 [70.8%]). The characteristics of the individual treatment groups were comparable.

Table 4 Demographic Characteristics (VEKTIS, FAS)

		High dose regimen (N=56)	Low dose regimen (N=54)	Placebo (N=58)	Total (N=168)
Age	Children (4-11 years)	43 (76.8%)	38 (70.4%)	46 (79.3%)	127 (75.6%)
	Adolescent (12-18 years)	13 (23.2%)	16 (29.6%)	12 (20.7%)	41 (24.4%)
	n	56	54	58	168
	Mean	9.1	9.6	8.9	9.2
	SD	3.3	3.4	3.2	3.3
	Median	9.0	9.0	8.0	9.0
	Min, Max	4, 17	4, 17	4, 17	4, 17
Sex	Male	44 (78.6%)	42 (77.8%)	46 (79.3%)	132 (78.6%)
	Female	12 (21.4%)	12 (22.2%)	12 (20.7%)	36 (21.4%)
Race	Caucasian	40 (71.4%)	38 (70.4%)	41 (70.7%)	119 (70.8%)
	Black	3 (5.4%)	5 (9.3%)	2 (3.4%)	10 (6.0%)
	Asian	11 (19.6%)	11 (20.4%)	13 (22.4%)	35 (20.8%)
	Other	2 (3.6%)	0	2 (3.4%)	4 (2.4%)

The majority of patients (n=110 [65.5%]) had both forms of VKC (see Table 7), i.e. limbal and tarsal VKC. The number of patients with limbal and/or tarsal VKC was comparable in all groups except in the low dose active group where patients with both forms were more numerous (39/54; 72.2%) and those with limbal VKC less numerous (2/54; 3.7%). Seasonal VKC was found in 75 patients (44.6%) and perennial VKC in 93 patients (55.4%). Mean time since diagnosis was 3.4 years (SD: 2.6). Most patients have used previous treatment for VKC (n=133 [79.2%]). The VKC history of the individual treatment groups was principally comparable.

Table 8 shows that the majority of patients had VKC Grade 3 (n=104 [61.9%]) and a CFS score of Grade 4 at baseline (n=145 [86.3%]). In 97 patients (57.7%), both eyes were eligible for analysis (see Table 8); the number of patients where only one eye was eligible was 34 patients (20.2%) with an eligible right eye and 35 patients (20.8%) with an eligible left eye, resulting in the analysis eye being the right eye in a total of 126 patients (75.0%). Baseline disease characteristics were comparable between the individual treatment groups except for the CFS score: with 14 patients (25.0%), the high dose group included more patients with CFS Grade 5 at baseline than the low dose or vehicle group with 5 (9.3%) and 4 patients (6.9%), respectively. Notably, 2 patients (3.4%) in the vehicle group did not meet the definition of eligible eye, since their mean values for the symptoms were below 60 (56.8 and 58.8, 51.5 and 50.8, respectively).

Table 5 History of VKC (VEKTIS, FAS)

		High dose regimen (N=56)	Low dose regimen (N=54)	Placebo (N=58)	Total (N=168)
Form of VKC	Limbal	8 (14.3%)	2 (3.7%)	7 (12.1%)	17 (10.1%)
	Tarsal	15 (26.8%)	13 (24.1%)	13 (22.4%)	41 (24.4%)
	Both	33 (58.9%)	39 (72.2%)	38 (65.5%)	110 (65.5%)
Type of VKC	Seasonal	29 (51.8%)	25 (46.3%)	21 (36.2%)	75 (44.6%)
	Perennial	27 (48.2%)	29 (53.7%)	37 (63.8%)	93 (55.4%)
Time since Diagnosis (years)	n	56	54	58	168
	Mean	3.5	3.6	3.1	3.4
	SD	2.5	2.8	2.6	2.6
	Median	3.0	2.9	2.2	2.6
	Min, Max	0, 12	0, 11	0, 11	0, 12
Use of prior VKC treatment	No	14 (25.0%)	8 (14.8%)	13 (22.4%)	35 (20.8%)
	Yes	42 (75.0%)	46 (85.2%)	45 (77.6%)	133 (79.2%)

Table 6 Disease Severity and Eligible / Analysis Eye (VEKTIS, FAS)

		High dose regimen (N=56)	Low dose regimen (N=54)	Placebo (N=58)	Total (N=168)
VKC grading (Bonini scale) at Baseline (Analysis eye)	Grade 3	32 (57.1%)	32 (59.3%)	40 (69.0%)	104 (61.9%)
	Grade 4	24 (42.9%)	22 (40.7%)	18 (31.0%)	64 (38.1%)
CFS score at Baseline (Analysis eye)	Grade 4	42 (75.0%)	49 (90.7%)	54 (93.1%)	145 (86.3%)
	Grade 5	14 (25.0%)	5 (9.3%)	4 (6.9%)	23 (13.7%)
Eligible Eye	OU (Both eyes)	28 (50.0%)	35 (64.8%)	34 (58.6%)	97 (57.7%)
	OD (Right eye)	13 (23.2%)	9 (16.7%)	12 (20.7%)	34 (20.2%)
	OS (Left eye)	15 (26.8%)	10 (18.5%)	10 (17.2%)	35 (20.8%)
	None	0	0	2 (3.4%)	2 (1.2%)
Analysis Eye	OD (Right eye)	40 (71.4%)	42 (77.8%)	44 (75.9%)	126 (75.0%)
	OS (Left eye)	16 (28.6%)	12 (22.2%)	14 (24.1%)	42 (25.0%)

Overall, the most frequent ocular histories were corneal opacity, hypermetropia, hordeolum and keratoconus, all in 3 patients (1.8%).

Prior to enrolment, most of the patients (149/169; 88.2%) had a specific treatment, and half of them (n=87) were having tear substitutes, corticosteroids (n=87) or other anti-allergic eye drops (n=97). Most frequent prior medication was olopatadine hydrochloride (34/169; 20.1%), fluorometholone (26/169; 15.4%) and ketotifen fumarate (25/169; 14.8%). Most frequently taken concomitant medications were desloratadine in 18 patients (10.7%) and salbutamol in 13 patients (7.7%). A total of 39.0% of the patients received concomitant treatment with antihistaminic agents.

In all treatment groups, the majority of patients had a compliance of 80 to 100% of treatment days, with 51 patients (89.4%) in the high dose group, 46 patients (85.3%) in the low dose group and 54

patients (93%) in the vehicle group. Accordingly, most patients were 80 to 100% compliant calculated on the intake of study medication drops, with 55 patients (96.5%) in the high dose group, 54 patients (96.4%) in the low dose group and 56 patients (96.6%) in the vehicle group.

Numbers analysed

A total of 169 patients were randomized into the study and were thus part of the RS; the same number of patients was included in the SS. The FAS consisted of 168 patients and the PPS of 159 patients. Notably, there was one patient initially assigned to the high dose regimen, who actually received initial treatment with vehicle because of incorrect study drug allocation.

Overall, 10 patients (5.9%) had a major protocol deviation, with 5 patients (8.8%) in the high dose group, 3 patients (5.5%) in the low dose group and 2 patients (3.5%) in the vehicle group. The overall most frequent protocol deviation was poor study drug compliance reported for 4 patients (2.4%). One patient initially assigned to the low dose group was excluded from the FAS due to violation of a main inclusion criterion, i.e. CFS score of 2 instead of 4 or 5.

Table 7 Number of Patients per Analysis Set (VEKTIS)

		High dose regimen	Low dose regimen	Placebo	Total
RS	Planned treatment	57	55	57	169
SS	Highest actual treatment	57	54	58	169
FAS	Initial actual treatment	56	54	58	168
PPS	Initial actual treatment	52	52	55	159

		High dose regimen in Period 2			Low dose regimen in Period 2		
		High dose regimen	Placebo	Total	Low dose regimen	Placebo	Total
FU-TS	Initial actual treatment	50	22	72	44	26	70

Follow-up Total Set (FU-TS) for the 8-month follow-up analyses of the exploratory endpoints and the safety analyses.

Outcomes and estimation

- **Primary composite endpoint: Penalty-adjusted CFS score at Month 4**

The primary composite endpoint was the average penalties adjusted CFS score over Period I (Month 4).

Monthly results are displayed by treatment groups, together with the mean penalty adjusted CFS score over Period I (Table 10). In all treatment groups, there was over time an increase of the penalty adjusted CFS score. There was a greater improvement over the 4 months in the high dose group (2.06; SD: 1.44) as compared to the 2 other groups.

The difference in the least square (LS) mean versus vehicle was 0.76 (95% CI: 0.26, 1.27) for the high dose group and 0.67 (95% CI: 0.16, 1.18) for the low dose group. This translates into an improvement of the penalty adjusted CFS score by 54% in the high dose group than in vehicle and 44% larger in the low dose group compared to vehicle. Both differences were statistically significant with p=0.007 for the high dose and p=0.010 for the low dose group. All sensitivity analyses for the comparison of active treatment vs. vehicle, included analyses for RS and PPS as well as using observed data for the FAS and analyses without taking unscheduled visits into account, confirmed these findings.

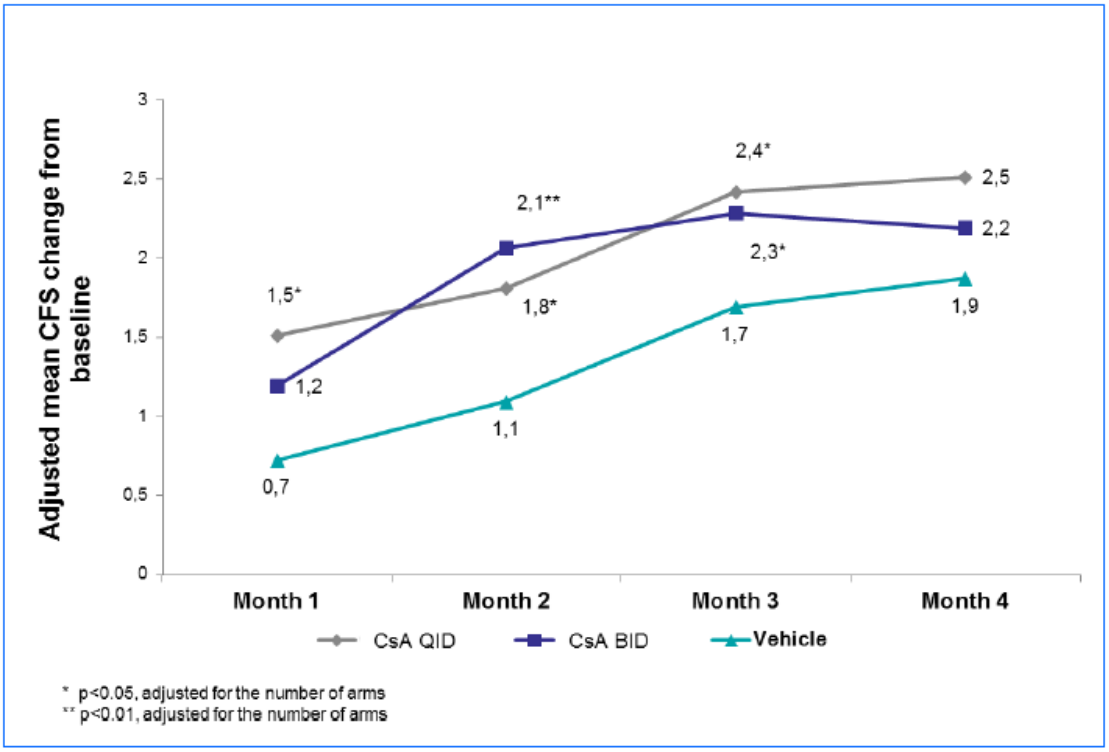
Table 8 Primary efficacy endpoint – VEKTIS (FAS)

Visit		High dose group (n=56)	Low dose group (n=54)	Vehicle (n=58)
Month 1	n	56	54	58
	Mean (SD)	1.51 (1.51)	1.19 (1.46)	0.72 (1.41)
	95% CI	1.10 - 1.91	0.79 - 1.59	0.35 - 1.09
	Median	1.00	1.00	0.00
	Min, Max	-1.0, 4.0	-2.0, 3.5	-1.0, 4.0
Month 2	n	56	54	58
	Mean (SD)	1.81 (1.64)	2.06 (1.56)	1.09 (1.40)
	95% CI	1.37 - 2.25	1.64 - 2.49	0.73 - 1.46
	Median	2.00	2.00	1.00
	Min, Max	-3.0, 4.5	-3.0, 4.0	-2.0, 4.0
Month 3	n	56	54	58
	Mean (SD)	2.42 (1.79)	2.28 (1.61)	1.69 (1.62)
	95% CI	1.94 - 2.90	1.84 - 2.72	1.26 - 2.12
	Median	3.00	3.00	2.00
	Min, Max	-2.0, 5.0	-2.0, 4.0	-2.0, 4.0
Month 4	n	56	54	58
	Mean (SD)	2.51 (1.79)	2.19 (1.65)	1.87 (1.59)
	95% CI	2.03 - 2.99	1.73 - 2.64	1.45 - 2.29
	Median	3.00	3.00	2.00
	Min, Max	-3.0, 5.0	-3.0, 4.0	-2.0, 4.0
Primary endpoint (average penalties adjusted CFS score over the 4 months)	n	56	54	58
	Mean (SD)	2.06 (1.44)	1.93 (1.37)	1.34 (1.22)
	95% CI	1.67 - 2.45	1.56 - 2.30	1.02 - 1.67
	Median	2.31	2.25	1.38
	Min, Max	-1.3, 4.6	-2.0, 3.9	-1.5, 4.0

Time course of the response

Primary endpoint results are supported further by the analysis of the time course of the response during Period I (Figure 3). The time course of the response to the high dose regimen was ascending and parallel to that of vehicle. This suggest that the onset of action is very fast and significant, i.e. as early as Month 1 ($p < 0.05$) and the benefit over the vehicle remains quite constant over time.

Figure 3 – Penalty adjusted CFS score over time – VEKTIS (FAS)



Contribution of the three components of the composite endpoint to the magnitude of the treatment effect (secondary endpoints)

To evaluate the contribution of the three components of the composite endpoint to the magnitude of the treatment effect, the primary model was applied separately to the three components: mean change from baseline in CFS, rescue medication and corneal ulceration. Absolute and relative contributions were both considered, and were expressed in percentage of the overall effect size (see Table 11).

CFS score was the main driver of the magnitude of the treatment effect, together with the need for rescue medication, the latter to a lesser extent. However, for the mean number of ulcer occurrences per month, there was no statistical difference between the active groups and the control group.

Rescue medication was used nearly two times more frequent in the vehicle group than in the active arms: 32.1% (18/56) of the patients in the high dose group and 31.5% (17/54) in the low dose group received at least one course of rescue medication compared to 53.4% (31/58) in the vehicle group. For all treatment groups at all time points, a large proportion of patients did not use rescue medication: ≥67.9% in the high dose group, ≥68.5% in the low dose group and ≥46.6% in the control group. The proportion of months during which at least one course of rescue medication was used was comparable in the 2 active treatment groups, and higher in the vehicle group. Differences in the number of courses compared to vehicle were statistically significant in favour of the high dose group at Month 1 (p=0.019) and Month 3 (p=0.044) and of the low dose group at Month 3 (p=0.044).

Table 9 Contribution of the 3 components of the primary endpoint to the magnitude of the treatment effect - Observed Data - 4-Month Randomised Period (FAS)

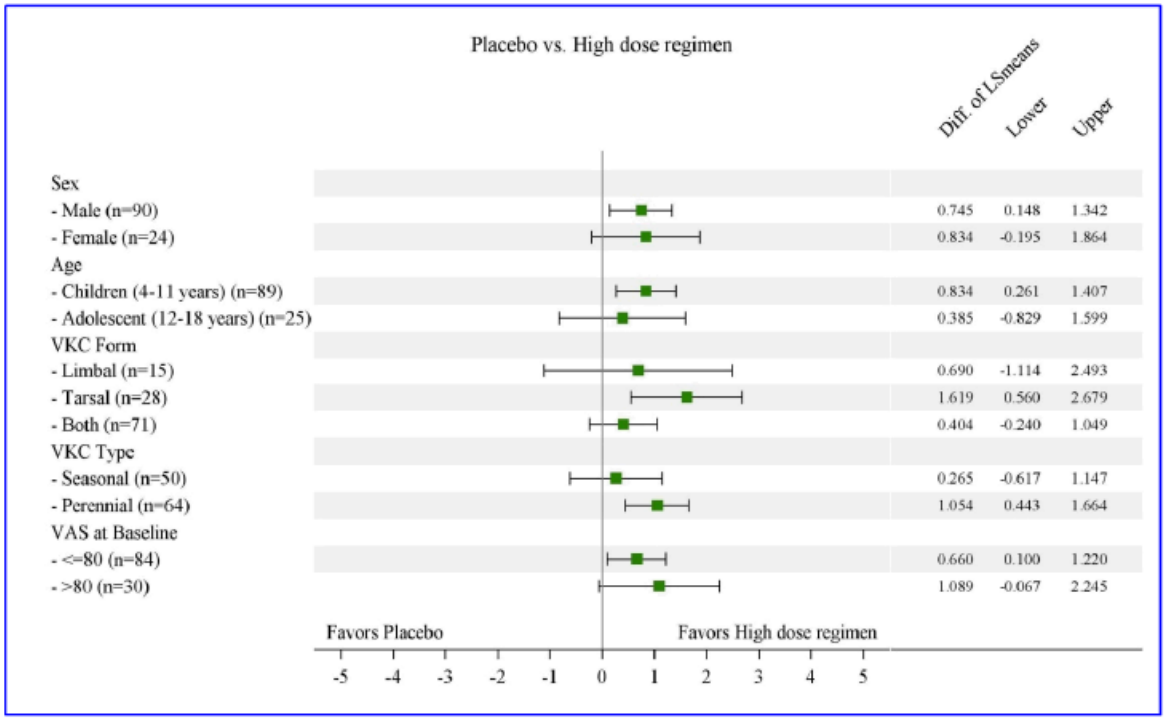
Endpoint		High dose – Vehicle	Low dose – Vehicle
Mean change from baseline of the mean CFS score per month**	LS mean (absolute contribution)	0.523	0.528
	95% CI	(0.109, 0.937)	(0.113, 0.943)
	Adjusted p-value*	0.014	0.014
	Relative contribution (%)	70.3%	77.6%
Mean number of rescue medication courses per month	LS mean (absolute contribution)	0.220	0.149
	95% CI	(0.068, 0.372)	(-0.003, 0.301)
	Adjusted p-value*	0.010	0.055
	Relative contribution (%)	29.6%	21.9%
Mean number of ulcer occurrences per month	LS mean (absolute contribution)	0.001	0.003
	95% CI	(-0.036, 0.038)	(-0.033, 0.040)
	Adjusted p-value*	0.966	0.966
	Relative contribution (%)	0.1%	0.5%

Note: Mean change from baseline of the mean CFS score per month = CFS score at baseline - mean of CFS score over 4 month, mean number of rescue medication courses per month = total number of rescue courses over 4 month / number of visits, Mean number of ulcer occurrences per month = total number of ulcer occurrences during the 4 months / number of visits.
* Hochberg procedure
** CFS non-adjusted for penalties

Primary treatment effect across subgroups

Subgroup analyses were performed to check homogeneity of effect across subgroups. This was purely descriptive. The analysis was done on pre-specified subgroups according to baseline disease status (seasonal or perennial VKC) and form (limbal and/or tarsal), baseline symptoms (less or more than 80 on VAS), sex and age (4-11; and 12-less than 18) and disease severity status (CFS grade 4 and 5). It was shown that both high and low dose regimens were generally favoured over vehicle in all subgroups and this effect was significant in at least one of the subgroups of each breakdown criterion. The Forest plot for the high dose regimen is shown in Figure 4.

Figure 4 – Penalty adjusted CFS across subgroups for CsA 0.1% QID vs. vehicle – VEKTIS (FAS)



- **Other endpoints**

CFS responder rate

The highest response rate was observed in the low dose group (33/54, 61.1%), followed by the high dose group (32/56, 57.1%) and vehicle (20/58, 34.5%). When compared to vehicle the odds ratios (95% CI) were 3.486 (1.576, 7.713) and 2.583 (1.207, 5.531) for the low and the high dose group, respectively. The difference was statistically significant in both cases (p=0.003 and p=0.013, respectively).

In line with a recommendation during a CHMP Scientific Advice, a more stringent definition of CFS responders was also explored to more specifically appreciate the impact of the treatment on corneal clearing, i.e. CFS graded 0 on the modified Oxford scale (instead of a reduction by 50% or more compared to baseline as per the original analysis). In this situation, a patient was defined as a responder if (1) he had a CFS graded 0 at Month 4, (2) he did not experience any ocular ulceration, (3) did not use any rescue medication in the last three months of treatment. Based on this definition, the greatest response rate was observed in the high dose group (19.6%) whereas the response rate was comparable in the low dose and control group (9.3% and 8.6%, respectively). The differences between active treatment and vehicle were not statistically significant with an odds ratio (95% CI) of 2.613 (0.842, 8.100) for the comparison of the high dose group versus vehicle and an odds ratio (95% CI) of 1.177 (0.319, 4.336) for the comparison of the low dose group versus vehicle (p=0.170 and 0.807, respectively).

Data for the responder rates were later re-analysed. The original analyses only took into account Month 2, 3 and 4 results. The re-analysis also included Month 1. Table 12 shows the results for the original responder definition (i.e. reduction of the CFS score by 50% or more compared to baseline).

Table 10 CFS responder rate over 4 Months of Treatment

Visit		High dose – QID (n=56)	Low dose – BID (n=54)	Vehicle (n=58)
Month 4	**n**	56		58
	Responder rate	31 (55.4%)	27 (50.0%)	16 (27.6%)
	Odds Ratios (vs. Vehicle)	3.279	2.798	-
	95% Confidence Limits	(1.501, 7.163)	(1.260, 6.211)	-
	p-value (LR test)*	**0.005**	**0.010**	-

Note: The treatment and the proportion of time spent on treatment within the VKC season are covariates.
*Hochberg procedure

Symptoms assessed using VAS

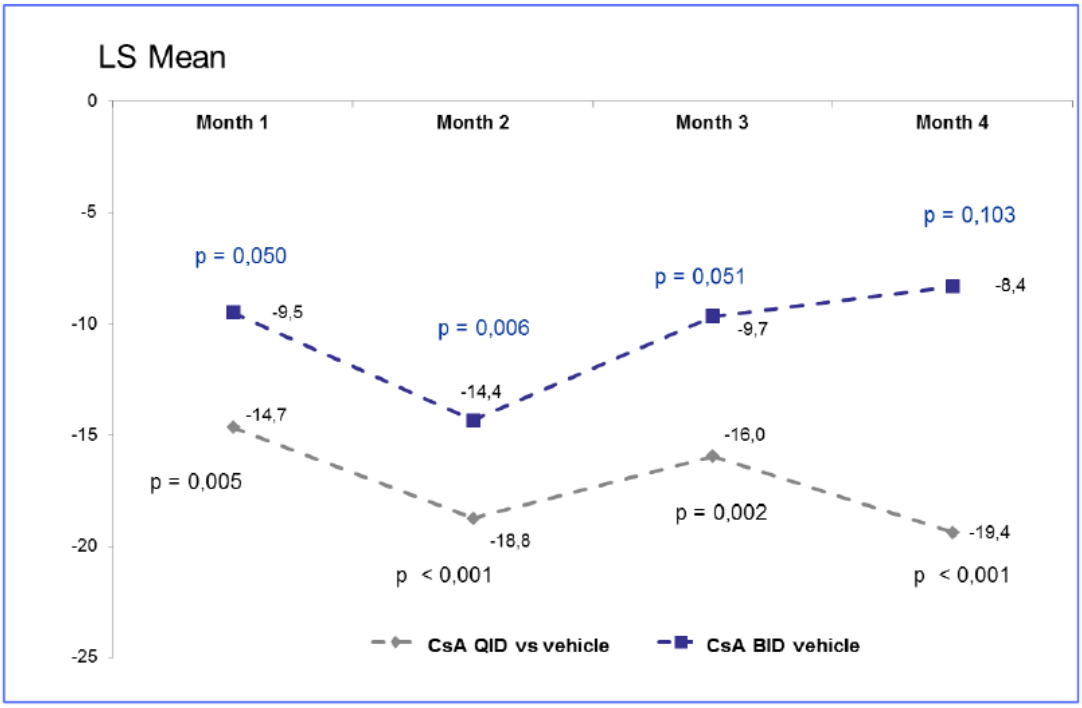
Throughout Period I, from baseline to Month 4, all VKC symptoms (i.e. photophobia, itching, tearing and mucous discharge) assessed based on a 100 mm VAS, improved in all 3 treatment groups. As shown by the LS mean values for the average of the 4 symptoms (Table 13 and Figure 5), the overall improvement was greatest in the high dose group (at baseline: 75.7 [SD: 11.2]; at Month 4: 26.0 [SD: 29.8]), followed by the low dose group (baseline: 72.6 [SD: 9.3], Month 4: 36.0 [SD: 32.4]) and the vehicle group (baseline: 72.7 [SD: 9.5]; at Month 4: 43.4 [SD: 27.3]).

Table 11 VAS Average of the 4 Symptom Scores – Difference in LS Mean versus Vehicle (FAS)

Visit/Source	p-value		High dose-Vehicle	Low dose-Vehicle
Treatment	<0.001			
Visit	<0.001			
Baseline	0.042			
Proportion of the evaluation period during the VKC season	0.203			
Treatment by visit	0.395			
Month 1		LS Mean	-14.684	-9.522
		95% CI	(-24.059, -5.310)	(-19.047, 0.003)
		Adjusted p-value*	0.005	0.050
Month 2		LS Mean	-18.776	-14.380
		95% CI	(-28.804, -8.747)	(-24.560, -4.199)
		Adjusted p-value*	<0.001	0.006
Month 3		LS Mean	-15.980	-9.697
		95% CI	(-25.550, -6.410)	(-19.418, 0.023)
		Adjusted p-value*	0.002	0.051
Month 4		LS Mean	-19.411	-8.355
		95% CI	(-29.307, -9.515)	(-18.402, 1.693)
		Adjusted p-value*	<0.001	0.103

Note: LMMRM with treatment, visit, and proportion of time within VKC season, baseline and patient as covariates
*: Hochberg procedure

Figure 5 - VAS Average of the 4 Symptom Scores – Difference in LS Mean versus Vehicle (FAS)



The average difference over vehicle across all 4 time points was 17.2 mm for the high dose group and 13.8 mm for the low dose group.

When comparing the 2 active treatments with vehicle, there was a statistically significant difference in the LS mean for the high dose group at all time points, whereas a statistically significant difference was only observed at Month 2 in the low dose group (p=0.006). At Month 4, the difference over vehicle in the high dose regimen was 2.3 higher than for the low dose regimen. For all symptoms and in all groups, the greatest improvement took place from baseline to Month 1.

When considering the evolution of each of the four symptoms (photophobia, tearing, mucous discharge and itching), a similar pattern was observed, and with a decrease over time (see Figure 6).

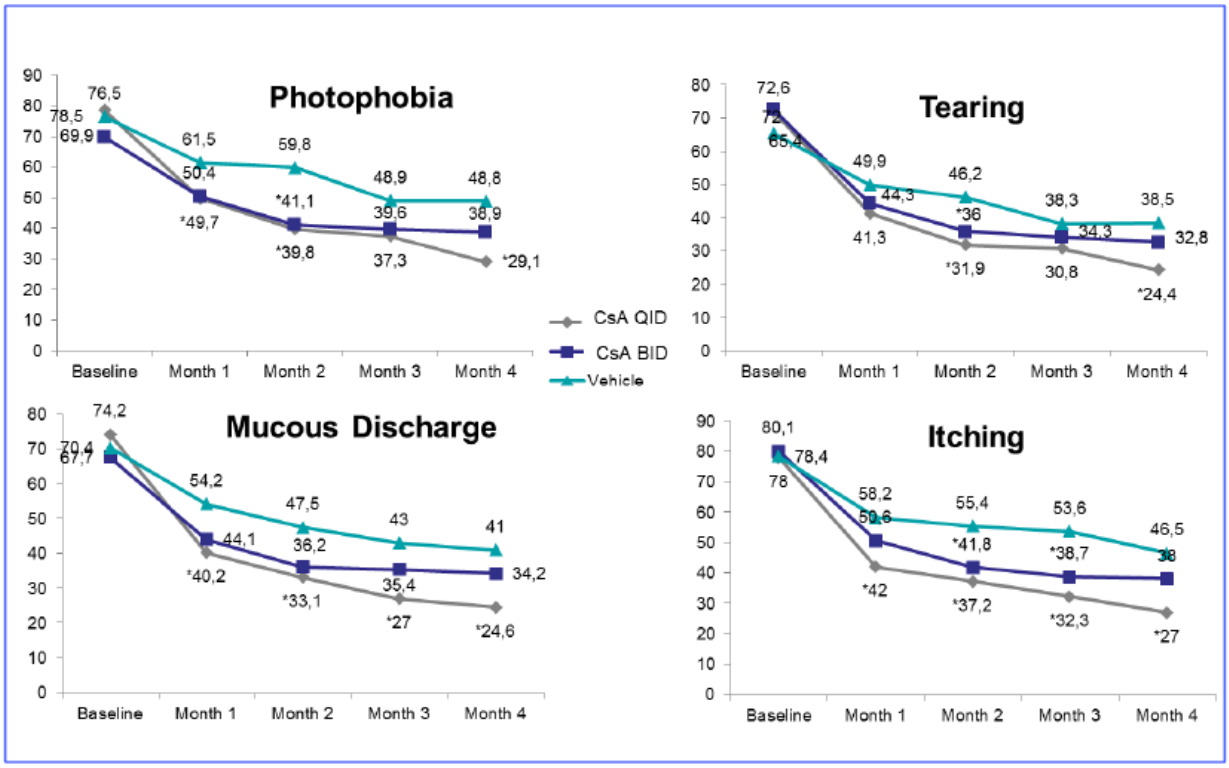
To complement the results for symptoms, the applicant performed *post-hoc* responder analyses as follows:

- Patients with an improvement from baseline by 50% of symptoms (average of the last three months), and
- Patients free from symptoms at Month 4.

The responder rates for improvement of symptoms (average of the findings for the 4 symptoms) by 50% were 27/56 (48.2%), 22/54 (40.7%), and 12/58 (20.7%) for the high dose, the low dose and vehicle, respectively. The odds ratios for the high and low dose compared to vehicle were 3.575 (95% CI: 1.569, 8.148; p=0.003) and 2.683 (95% CI: 1.151, 6.254; p=0.020).

The responder rates for freedom of symptoms (average of the findings for the 4 symptoms) at Month 4 were 8/56 (14.3%), 4/54 (7.4%), and 1/58 (1.7%) for the high dose, the low dose and vehicle, respectively. The odds ratios for the high and low dose compared to vehicle were 9.564 (95% CI: 1.152, 79.367; p=0.017) and 5.029 (95% CI: 0.542, 46.663; p=0.110).

Figure 6 – VAS Scores by Symptoms – Evolution over Time (FAS)



Use of artificial tears

Overall, monthly usage of artificial tears, which was capped at up to 4 times a day, remained low throughout Period I. Highest percentages of patients with tear usage were found at Month 1 with 4/56 patients (7.1%) in the high dose group, 5/54 patients (9.3%) in the low dose group and 11/58 patients (19.0%) in the control group.

Health related quality of life (Quick questionnaire)

A decrease from baseline to Month 4 in the scores of both domains (symptoms and daily activities) of the Quick questionnaire was found in all treatment groups, thus indicating an improvement in patient quality of life (Table 14).

During the 4-month double-masked period (Period I), a statistically significant difference over vehicle was found at all time points for the high dose group for both domains (symptoms and activities of daily life), except for daily activities at Month 1. For the low dose group, significant differences were only found at Month 2 (p=0.003).

Table 12 Quick Questionnaire - change from baseline – Period I (FAS)

Domain	Visit/Source	p-value*		High dose - Vehicle	Low dose - Vehicle
Domain: Symptoms					
Treatment		0.002			
Visit		<0.001			
Baseline		<0.001			
Proportion of the efficacy evaluation period spent during the VKC season		0.147			
Treatment by visit		0.144			
	Month 1		LS Mean	-9.684	-6.744
			95% CI	(-17.729, -1.639)	(-14.979, 1.491)
			Adjusted p-value*	0.037	0.108
	Month 2		LS Mean	-15.646	-12.585
			95% CI	(-23.585, -7.707)	(-20.714, -4.455)
			Adjusted p-value*	<0.001	0.003
	Month 3		LS Mean	-12.075	-6.462
			95% CI	(-19.812, -4.337)	(-14.391, 1.467)
			Adjusted p-value*	0.005	0.110
	Month 4		LS Mean	-8.766	-3.817
			95% CI	(-16.403, -1.129)	(-11.646, 4.013)
			Adjusted p-value*	0.049	0.338
Daily Activities					
Treatment		0.017			
Visit		0.001			
Baseline		<0.001			
Proportion of the efficacy evaluation period spent during the VKC season		0.061			
Treatment by Visit		0.732			
	Month 1		LS Mean	-7.995	-6.129
			95% CI	(-16.565, 0.576)	(-14.845, 2.588)
			Adjusted p-value*	0.135	0.167
	Month 2		LS Mean	-9.321	-10.076
			95% CI	(-18.525, -0.117)	(-19.427, -0.725)
			Adjusted p-value*	0.047	0.047
	Month 3		LS Mean	-11.425	-6.917
			95% CI	(-19.569, -3.281)	(-15.207, 1.373)
			Adjusted p-value*	0.012	0.101
	Month 4		LS Mean	-10.330	-5.070
			95% CI	(-17.462, -3.198)	(-12.348, 2.208)
			Adjusted p-value*	0.009	0.171

Notes: Quick Questionnaire = (total score - number of non-missing score) / (number of non-missing score * 2) * 100 in each domain; Minimum score is defined as 0 (Positive) and maximum is 100 (Negative); LMMRM with treatment, visit, proportion of time within VKC season, baseline, treatment by visit and patient as covariates.
*: Hochberg procedure

Global assessment by the Investigator

In all treatment groups, the investigator assessed the treatment as satisfactory or very satisfactory for the majority of patients. At Month 4, 42/49 (85.7%) patients in the high dose group, 37/43 (86.0%) patients in the low dose group and 33/48 (68.8%) patients in the vehicle group had a positive global assessment by the Investigator. Though numerical advantages for the active treatment groups exist, the frequency distributions did not differ statistically significant from vehicle (p=0.080 for both high and low dose regimens).

Longer Term Use (exploratory efficacy assessment)

Patients involved in Period II were divided in three different subgroups:

- Subgroup A: patients who stopped the treatment at Month 4 and never used it again until Month 12.
- Subgroup B: patients who did not stop their treatment at Month 4 and continued it up to Month 12.
- Subgroup C: patients who used active treatment in an intermittent manner during the “on demand” period.

Description of the 8-month efficacy data was limited to analyses of subgroups B and C (with Month 4 measurements as baseline).

During Period II, 72 patients in the high dose total group (including 22 patients originally assigned to vehicle) and 70 patients in the low dose total group (including 26 patients originally assigned to vehicle) were allowed to use treatment, as required, until the next allergic season. Only few withdrawals occurred: one in the high dose total group (1.4%); and 5 in the low dose total group (7.1%).

Subgroup B consisted of 42 patients in the high dose group (including 13 patients originally assigned to vehicle) and 42 patients in the low dose group (including 17 patients originally assigned to vehicle).

Subgroup C consisted of 26 patients in the high dose group (including 6 patients originally assigned to vehicle) and 23 patients in the low dose group (including 8 patients originally assigned to vehicle).

Overall, CFS scores remained stable during Period II for subgroup B patients. Patients who switched from vehicle to active treatment showed an improvement after Month 4. In the high dose group, the mean change from baseline was -0.81 (SD: 0.90) at Month 6 and - 1.27 (SD: 1.36) at Month 12/Early termination for this subset of patients. In the low dose group, the trend for improvement of the CFS score was found as well. The change from baseline at Month 6 was greater compared to the high dose group with -1.17 (SD: 1.47). At Month 12/Early termination, it was smaller with -0.93 (SD: 1.71). In subgroup C, a slight increase of CFS score was noted after Month 8 suggesting a worsening of the disease.

VAS symptom scores remained overall stable during Period II. In subgroup B, additional improvement was seen after Month 4, especially in patients switching from vehicle to active treatment. Overall, the high dose total group had an average mean change of the symptom score from baseline of -9.3 (SD: 30.4). In the low dose total group, the symptoms showed an improvement from Month 4 to Month 6 with a mean change of the VAS score from baseline of -10.6 (SD: 20.4), remaining stable at subsequent visits.

For the group of patients who switched from vehicle in the randomized period to active treatment in the follow-up period, the changes from baseline indicate an improvement of the symptoms in both

follow-up treatment groups. In the high dose group, the symptoms continuously improved, with greatest mean change from baseline of -17.3 (SD: 28.7) at Month 12/Early termination. In the low dose group, a trend for improvement was found as well up to Month 8 with a mean change from baseline of -17.9 (SD: 20.1).

In subgroup C, there was no improvement of symptoms for the total groups. VAS scores increased till the end of Period II.

Overall use of rescue medication was low; the majority of patients (usually more than 80%) did not take rescue medication at all at any time point. The same trend was seen in subgroups B and C.

The Quick questionnaire showed stable results in patients' quality of life from baseline during the course of Period II for both symptoms and daily activities, overall and in subgroup B. In subgroup C, changes from baseline suggest a worsening in symptoms and daily activities.

In the Investigator's global assessment, treatment was reported being either 'very satisfactory' or 'satisfactory' for the majority of patients, and the same trend was seen in subgroups B and C. Percentages of positive global assessments were high (>78%) in both treatment groups. In subgroup B, patients who switched from vehicle to active treatment had a higher percentage of positive assessments with 100% in the high dose and 85.7% (12/14) in the low dose group. Subgroup C showed the same trends.

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 13 Summary of Efficacy of VEKTIS

Title: **Multicenter, randomized, double-masked, 3 parallel arms, placebo controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis**		
Study identifier	Company Protocol Number: NVG09B113 EudraCT Number: 2012-005060-10	
Design	Multicenter, randomized, double-masked, vehicle controlled Phase 3 trial	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 months not applicable 8 months
Hypothesis	Superiority	
Treatments groups	High dose regimen	1 drop of CsA (NOVA22007) 1 mg/mL (0.1%) QID in each eye for 4 months, 57 randomised patients
	Low dose regimen	1 drop of CsA (NOVA22007) 1 mg/mL (0.1%) BID in each eye for 4 months, 55 randomised patients
	Vehicle	1 drop of vehicle (same formulation as NOVA22007 but excluded the active substance) QID in each eye for 4 months, 57 randomised patients

Endpoints and definitions	Composite Primary endpoint	Penalty adjusted CFS score	Composite efficacy score at 4 months, defined as the mean of the 4 efficacy scores taken at each monthly visit, based on the following equation: *Patient's score at month X = CFS (Baseline) – CFS (Month X) + penalty(ies).* A penalty of -1 was applied for use of rescue medication and in case of corneal ulceration.
	Secondary endpoint	CFS responders	Rate of responders at Month 1[#], 2, 3 and 4. Responders were defined as patients (1) with a CFS score equal or smaller than 50% of the baseline CFS, (2) who did not withdraw from the study for a reason possibly due to treatment, (3) free from occurrence of ulceration and (4) free from use of rescue medication. [#] *Inclusion of Month 1 was done post-hoc in response to a CHMP request.*
	Secondary endpoint	VAS symptom score	Change of the average of 4 symptom scores (photophobia, tearing, itching and mucous discharge) at Month 4 compared to baseline, assessed using a 100 mm VAS
	Secondary endpoint	Rescue medication	Proportion of months with at least 1 use of rescue medication
Database lock	Date of Last Patient Completed: 01 Feb 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Analysis Population: Full Analysis Set, i.e. all randomized patients, potentially excluding few patients corresponding to the failure to take at least 1 dose of study medication and very early withdrawal (first week after randomization) definitely not related to study medication and leading to the lack of any post randomization data. Time point: 4 months			
Descriptive statistics and estimate variability	Treatment group	High dose regimen	Low dose regimen	Vehicle
	Number of subject	56	54	58
	Penalty adjusted CFS score (mean)	2.06	1.93	1.34
	SD	1.44	1.37	1.22
	CFS responders (%)	55.4	50.0	27.6
	VAS symptom score (change in LS mean, mm)	49.7	36.6	29.3
	Rescue medication (%)	32.1	31.5	53.4
	95% CI	0.203, 0.460	0.195, 0.456	0.399, 0.667

		Comparison groups	(1) High dose regimen vs. vehicle (2) Low dose regimen vs. vehicle
	Penalty adjusted CFS score	Difference in LS mean	(1) 0.76 (2) 0.67
		95% CI	(1) 0.26, 1.27 (2) 0.16, 1.18
		P-value	(1) 0.007 (2) 0.010

	CFS responders	Odds ratio	(1) 3.279 (2) 2.798
		95% CI	(1) 1.501; 7.163 (2) 1.260; 6.211
		P-value	(1) 0.005 (2) 0.010
	Rescue medication	Difference in mean change of rescue medication courses per month	(1) 0.220 (2) 0.149
		95% CI	(1) 0.068, 0.372 (2) -0.003, 0.301
		P-value	(1) 0.010 (2) 0.055
	VAS symptom score	Difference in LS mean	(1) -19.41 (2) -8.36
		95% CI	(1) -25.55, -6.41 (2) -18.40, 1.69
		P-value	(1) <0.001 (2) 0.103
Notes	Rescue treatment consisted of dexamethasone 0.1% eye drops provided by the sponsor, 1 drop 4 times daily for 5 days. A maximum of 2 courses of rescue between 2 scheduled visits during the 4-month treatment period and a maximum of 4 courses of rescue between 2 scheduled visits during the follow-up period were allowed. Patients involved in VEKTIS were allowed to use unpreserved tear substitutes up to 4 times a day only in case of worsening of the VKC symptoms and inability to have a visit for rescue corticosteroid therapy prescription. The analysis eye was the worst eye at inclusion. The worst eye was defined as the eligible eye with the highest Oxford score for corneal staining at Baseline. In case both eyes had the same score at Baseline the right eye was considered.		

2.5.3. Supportive study(ies)

Study NVG05L101 (NOVATIVE): A Phase II/III, multicenter, randomised, parallel group, dose ranging, controlled trial of efficacy and tolerance of NOVA22007 (ciclosporin A) 0.05% and 0.1% ophthalmic cationic emulsion versus vehicle in patients with vernal keratoconjunctivitis

The NOVATIVE study compared the efficacy, safety, and tolerability of 2 dose regimen, NOVA22007 0.05% QID and NOVA22007 0.1% QID with vehicle in patients with active VKC. Moderate to severe VKC patients were recruited into this study. To be included into the study, patients had to be at least 4 years of age and needed to have at least in at least one (the same) eye two signs (giant papillae with a diameter ≥ 1 mm on the upper tarsal conjunctiva and a superficial keratitis), and two ocular symptoms (burning/stinging, tearing, itching, pain, sticky eyelids, foreign body sensation, mucus discharge, and/or photophobia, scored from 0 to 3) with at least one score >2, and an hyperaemia score ≥ 2.

The study duration was 4 months overall, divided into two treatment periods:

- Period I was a 4-week three parallel-groups, vehicle-controlled treatment period. Patients were randomised on a 1:1:1 basis to one of the three treatment groups: NOVA22007 0.05%, NOVA22007 0.1% or vehicle one drop in both eyes four times daily.
- Period II, which followed Period I was a 3-month, two parallel group treatment period. Following completion of Period I all patients received NOVA22007 0.05% or 0.1%, four times or twice daily (depending on tolerance) in both eyes.

One hundred and eighteen (118) patients were randomised. Forty (40) patients were randomised to receive vehicle, 39 to receive NOVA22007 0.05% and 39 to receive NOVA22007 0.1% QID. All patients were treated, and included in the safety analysis and in the FAS. Overall, more males (96/118; 81.4%) than females were recruited. The mean age was 8.5 years (range 4 to 21 years). In total, 37.3% of patients had clinically significant non-ophthalmic history. Of these, 16.9% had respiratory, thoracic and mediastinal disorders, including 12.7% of patients who had asthma. In total, 14.4% of patients had an immune system disorder and 15.3% had skin and subcutaneous tissue disorders (the NOVA22007 0.05% group had nearly double the number of patients with allergy and skin disease compared to the other groups).

At the end of Period I, 111 patients (94.1%) were still in the study and all entered Period II of the trial: 36 patients who received vehicle during Period I (of which 19 received NOVA22007 0.05% in Period II and 17 NOVA22007 0.1%), 39 patients who remained in the NOVA22007 0.05% group and 36 remaining in the NOVA22007 0.1% group.

The primary objective was to demonstrate superiority of NOVA22007 1 mg/mL over vehicle based on the effect on symptoms using a semi-quantitative scale, the BenEzra scale (BenEzra 1986). Change from baseline at Month 1 in the overall rating of ocular symptoms, which would have indicated an improvement, was used as the primary endpoint. The study did not meet its primary objective with no statistically significant difference being shown for either of the active arms compared to vehicle ($p=0.2450$ and $p=0.2664$).

However, a significant benefit in favour of NOVA22007 was shown in secondary endpoints evaluating objective ocular signs of VKC under the slit lamp. At Month 1, a statistically significant improvement in the overall rating of objective signs of VKC for patients in the 2 active groups ($p=0.04$ and $p=0.02$ with NOVA22007 low dose and NOVA22007 high dose, respectively) was observed. Furthermore, both NOVA22007 doses provided a statistically significant improvement in CFS ($p=0.003$ and 0.014 for NOVA22007 low dose and NOVA22007 high dose, respectively) assessed using the Oxford scale.

Results of a post-hoc analysis of the NOVATIVE study in 45 patients with active VKC and severe keratitis (CFS ≥ 4 on the modified Oxford scale) suggested a potential for a greater benefit with the 0.1% dose of NOVA22007 over the 0.05% dose. At Month 1, mean improvement in CFS was greater with the high dose with a reduction of 2.14 compared to a reduction of 1.94 with the low dose and a reduction of 1.14 with the vehicle ($p=0.009$ and $p=0.031$ vs. vehicle, respectively). The effect size was greater for both high dose and low dose regimens compared to the entire study population (with moderate to severe VKC). Greater improvements over vehicle was also shown for both the 0.1% and the 0.05% dose for the primary efficacy endpoint, the overall rating of objective symptoms and for the secondary endpoints improvement in CFS and the overall rating of objective VKC signs at Month 1.

2.5.4. Discussion on clinical efficacy

The assessment of the clinical efficacy of Verkazia in the treatment of VKC was mainly based on the results of the VEKTIS study, a randomised, double-blind, vehicle controlled trial investigating the efficacy and safety of CsA 0.1% eye drops BID and QID in patients with active, severe disease. Supportive data were available from NOVATIVE, a phase 2/3 trial in moderate to severe VKC patients.

During the clinical development, the eye drops formulation was optimised, and the excipient benzalkonium chloride (BAK) was changed to cetalkonium chloride (CKC). Given that the new CKC containing formulation, which is proposed for commercial use, is identical to that of Ikervis (approved in the EU since 2015 for the treatment of severe keratitis in dry eye disease) and was used in the pivotal Phase 3 VEKTIS study, the change in formulations did not raise any particular concern.

Design and conduct of clinical studies

Both VEKTIS and NOVATIVE studies recruited children and adolescents with VKC, whereby patients in VEKTIS had severe disease defined as grade 3 or 4 of Bonini scale as well as a compromised cornea (grade 4 or 5 on the modified Oxford scale). The choice of the patient population in the pivotal VEKTIS trial was based on a *post-hoc* subgroup analysis in NOVATIVE, which had shown more promising results in the subset of patients with severe keratitis compared to the entire moderate to severely affected NOVATIVE study population. VEKTIS was designed as a confirmatory trial to support use of CsA 0.1% in patients with severe disease and is therefore the focus of this section.

Overall, the study population in VEKTIS was considered well defined and representative of the intended target population of Verkazia. The age range applied for was in line with the age range (4 to less than 18 years) studied in VEKTIS. However, the CHMP noted that there are cases where the disease continues into adulthood. The fact that no data were available from (young) adults has been reflected in the SmPC of Verkazia. Furthermore, given that VKC patients with severe disease and corneal involvement have the highest risk for sight threatening complications and ultimately vision loss, the target population was agreed to be an adequate choice for treatment with an immunomodulator and in line with the current use of CsA eye drops in clinical practice.

The limited study sizes with 169 patients and 118 patients in VEKTIS and NOVATIVE, respectively, were considered justified given the rarity of the disease. However, the small number of patients made the interpretation of the results difficult at times (see efficacy data below).

Two CsA strength/doses were tested in either study. NOVATIVE compared CsA 0.1% QID and 0.05% QID, whereas VEKTIS included CsA 0.1% QID and 0.1% BID. The choice of the 0.1% strength in VEKTIS was largely based on *post-hoc* analyses of the NOVATIVE study data, suggesting a potential for a greater benefit with the 0.1% dose over the 0.05% dose in the subset of patients with severe disease. Vehicle was used as comparator. The use of an active comparator had been ruled out by the applicant since no appropriate one existed for this condition. Similarly, artificial tears, which do not have any pharmacological properties and are usually a background treatment in VKC, were not considered suitable. Rather, use of artificial tears was assessed as a secondary endpoint. Corticosteroids were also excluded due to their local side effects in particular when used long-term. Overall, the choice of CsA doses/strengths and of the control was considered acceptable; it had previously been discussed in a CHMP scientific advice.

The design and conduct of the pivotal VEKTIS study was also considered acceptable, although some questions were raised in relation to the efficacy endpoints. In VEKTIS, efficacy was primarily assessed based on a composite score with a focus on signs, based on the change from baseline in keratitis/ocular surface damage measured as CFS and adjusted by penalties for the use of rescue medication and the occurrence of corneal ulcers. The lack of validation of this endpoint was ultimately accepted given the absence of any validated endpoints in this disease setting. However, while all subcomponents were agreed to be clinically relevant, progression to corneal ulcers could be expected to be rare given that use of rescue treatment was allowed in case of progression. In this context, the analyses evaluating the relative contribution of each of the subcomponents and to show consistency of the effect across the components were considered important. Furthermore, the choice of the penalty score of 1 was rather arbitrary and has not been adequately justified by the applicant. Sensitivity analyses modifying the weighting of the penalty were therefore requested by the CHMP during the course of the procedure.

Other endpoints including responder analyses, improvement of symptoms and need for corticosteroid rescue treatment were generally considered useful to complete the picture of the treatment effect.

Efficacy data and additional analyses

Patient characteristics were generally well balanced across the study groups in VEKTIS. As would be expected considering the condition, there was a preponderance of male Caucasians. The majority of VKC patients were children aged 4-11 years (75.6%) compared to 24.4% of adolescents, which is in line with the clinical presentation of the disease which usually resolves after puberty. The majority of patients (65.5%) had both forms of VKC, i.e. limbal and tarsal VKC. The number of patients with limbal disease only was somewhat lower in the low dose active group with 3.7% compared to 14.3% and 12.1% in the high dose group and the vehicle group, respectively. However, at the same time, combined limbal and tarsal forms were more frequent in the high dose (72.2%) and the vehicle group (65.5%) compared to the low dose group (58.9%).

VEKTIS met its primary endpoint with both the high dose CsA group (0.1% QID) and the low dose CsA group (0.1% BID) being superior to vehicle. Penalty adjusted CFS scores increased over the first 4 months in both active groups to a larger extent than for vehicle (difference in the LS mean vs. vehicle was 0.76 and 0.67 for the high and the low dose group, respectively) and the difference was statistically significant (p=0.007 and p=0.010). Sensitivity analyses modifying the weighting of the penalty were conducted *post-hoc* assigning a penalty of 2 to the use of rescue medication and 1 for ulceration and the other way round (i.e. score of 1 assigned to rescue medication and 2 to ulceration). The outcome of these analyses remained in favour of CsA with a statistically significant difference to vehicle for both low and high dose groups. However, there were doubts on how to interpret the results of the primary endpoint in terms of clinical relevance.

The CFS score was the main driver of the magnitude of the treatment effect, together with the need for rescue medication to a lesser extent. The CFS score accounted for 70.3% of the effect size of the high dose and 77.6% of the effect size of the low dose. The contribution of the number of rescue medication courses to the magnitude of effect was between 20% and 30% for the two active arms. For these two components, the treatment effect was toward the expected directions, i.e. an improvement in corneal health and less need of corticosteroid rescue medication with the active treatment groups compared to vehicle. However, no effect for the third subcomponent of the primary endpoint, corneal ulceration, was seen due to the rare occurrence of ulcers within the 4 months evaluation period. As previously mentioned, this was not unexpected given the possibility to use recue treatment in case of disease progression. At the same time, no conclusion on the efficacy of Vekarzia in the prevention of disease progression to corneal ulceration was possible.

Subgroup analyses on the primary endpoint by gender, age (children versus adolescents), VKC form/type and VAS at baseline all showed at least a trend in favour of Verkazia compared to vehicle. However, a smaller effect size was observed for adolescents compared to children, for seasonal disease compared to perennial disease and for limbal disease/both forms compared to tarsal disease. However, the interactions were not found to be statistically significant for any of the aforementioned comparisons and given that generally the point estimates were in favour of active treatment and that some of the subgroups were small in size, which may have contributed to a chance finding, the issue was not further pursued.

A benefit of Verkazia with regards to corneal health was further supported by CFS responder analyses showing a greater response rate in the high and low dose groups (57.1% and 61.1%) compared to vehicle (34.5%) at Month 4. The difference to vehicle was statistically significant for both active groups (p=0.013 and p=0.003). When including Month 1 into the analysis (originally omitted as it was hypothesised that many patients would take rescue medication during the first days of treatment and therefore would have been considered non-responders), the difference between active treatment and vehicle remained with a responder rate of 55.4%, 50.0% and 27.6% in the high dose group, low dose group and vehicle, respectively (p=0.005 and 0.010).

Given the difficulties in interpreting the clinical relevance of the primary composite endpoint, the CFS responder analyses, in particular the one incorporating response rates at Month 1, were considered more relevant in order to understand the actual benefits of treatment with Verkazia. An improvement of the CFS score by 50% or more from baseline without the need for rescue treatment or occurrence of ulceration, as used for the responder definition, was considered by the CHMP to be clinically meaningful in the proposed target population of patients with severe VKC. The observed increase in the response rates with both high and low CsA dose compared to vehicle (odds ratio of 3.279 and 2.798 for the high and low dose group, respectively) thus supported a clinically relevant treatment benefit of Verkazia.

The analysis of the use of rescue medication also supported a beneficial effect of CsA 0.1% QID and BID. Rescue medication was used nearly twice as often by patients in the vehicle group compared to patients in the active arms. Overall, 32.1% (18/56) of the patients in the high dose group and 31.5% (17/54) in the low dose group received least one course of rescue medication compared to 53.4% (31/58) in the vehicle group. The difference versus vehicle in the mean number of rescue medication courses per months was statistically significant for the high dose group ($p=0.010$) and close to significance for the low dose group ($p=0.055$).

The study also showed an improvement in subjective symptoms, as measured using a 100mm VAS score including 4 VKC symptoms, photophobia, tearing, itching and mucous discharge. Throughout the 4 months evaluation period, all VKC symptoms improved from baseline irrespective of the treatment received. For all symptoms and in all groups, the greatest improvement took place from baseline to Month 1. The overall improvement was greatest in the high dose group. When comparing the 2 active treatments with vehicle, the difference in the LS mean change of the average symptom score was -19.4mm ($p<0.001$) and -8.4mm ($p=0.103$) for the high dose and the low dose regimen. The results by symptom were consistent with the overall symptom score showing a greater improvement for each of the individual symptom scores with active treatment compared to vehicle. The effect size at Month 4 for each of the symptoms and overall was generally within the range of 8-10mm for the low dose and 14-20mm for the high dose, which was accepted by the CHMP as clinically relevant. *Post-hoc* symptom responder analysis (improvement from baseline by 50% or total freedom of symptoms) provided consistent findings supportive of a beneficial effect of Verkazia.

An at least numerically favourable effect of CsA over vehicle was also observed with regards to the use of artificial tears (although the use of these was capped at up to 4 times a day and remained low throughout the study), as well as for the global assessment by the investigator, albeit most of the between-group comparisons were not statistically significant.

Quality of life improved from baseline in all treatment groups both with regards to symptoms and daily activities and a greater improvement was observed for active treatment compared to vehicle with the largest effect achieved in the high dose group (statistically significant at almost all time points for both domains).

Long-term data gathered during the 8 months follow-up period of the study suggested maintenance of the treatment effect in patients who continued active treatment after the initial 4 months evaluation period. Of the 169 patients randomized into VEKTIS, 142 continued into the follow-up period. These were patients who enrolled early in the study and for whom the VKC allergy season was still ongoing as well as patients who still presented signs and symptoms of VKC according to the investigator's judgment. Furthermore, patients who experienced a recurrence of active VKC or a worsening in VKC symptoms following the discontinuation of study treatment outside of the VKC allergy season during the remaining time in the 8-month follow-up period were allowed to resume active treatment. Overall, 82/142 patients did not stop their treatment at Month 4 and continued it up to Month 12.

Based on the data from the long-term follow-up period, it was agreed that Verkazia could be taken during the VKC season and that treatment may be continued if signs and symptoms of VKC persist after the end of the season. Further clarification was provided that if signs and symptoms resolve, treatment can be discontinued and reinitiated upon reoccurrence. The fact that there was no experience with continuous use of Verkazia for a period longer than 12 months was also reflected in the SmPC.

Overall, the results of VEKTIS were consistently in favour of CsA 0.1% across the various efficacy endpoints (the only exception being progress to corneal ulcers), although statistical significance was not always reached. Therefore, the study results in their totality were considered supportive of a clinically meaningful beneficial effect of Verkazia in the target population of patients with severe VKC. Beneficial effects were seen with both the high dose (4 drops a day) and the low dose (2 drops a day) CsA treatment regimen. When comparing the two regimens, QID dosing had a numerically better outcome with regards to symptomatic improvement, whereas a slightly greater effect in terms of CFS responder rate (excluding Month 1) and need for rescue treatment was observed for BID dosing. In this context, the CHMP noted that QID administration may be difficult to realise, in particular for children going to the nursery or school. In VEKTIS, noon and afternoon administrations were performed by parents who went to school or by a school nurse, and compliance was high. However, in real-life this may constitute a challenge for many parents/schools and may be difficult to maintain over prolonged periods. A less frequent instillation (morning and evening only) would be expected to be more convenient and increase compliance.

Altogether, given the seasonal increase in signs and symptoms of the condition a recommendation for QID dosing during VKC season was considered acceptable. Thereafter (at the end of the season), patients will have the option to continue treatment at a reduced (BID) dose, once adequate control of signs and symptoms is achieved. This is in line with the expectation of a reduction in disease severity when the hot season is declining. It is furthermore recommended that Verkazia should be discontinued after signs and symptoms are resolved, and reinitiated upon their recurrence.

2.5.5. Conclusions on the clinical efficacy

Overall, the CHMP was of the view that the available clinical efficacy data were adequate to support the present application. In light of the consistent improvements observed with CsA 0.1% in VEKTIS across a number of outcome measures including both VKC signs (most notable CFS responders) and symptoms, the CHMP considered that a clinically relevant benefit of Verkazia had been demonstrated in the treatment of severe VKC in children from 4 years of age and adolescents.

2.6. Clinical safety

The review of the safety of Verkazia includes data from two clinical trials performed in patients with VKC. The pivotal Phase 3 VEKTIS study included patients with severe VKC and investigated 2 doses of CsA 0.1% (QID and BID). The Phase 2/3 NOVATIVE study included patients with generally milder disease although some of them (45/118) also had severe VKC. This study investigated CsA 0.05% and 0.1%, both QID.

For a summary of the study design and methods, see sections 2.5.2. and 2.5.3.

Safety data were pooled based on the safety populations of each of the individual studies; i.e. randomised patients who took at least one dose (2 or 4 drop per day) of CsA. Data were pooled into two different analysis cohorts.

- The ‘Double masked study cohort’ (n=287) including patients from the double masked period of the VEKTIS study (4-month period) and NOVATIVE study (1-month period) in order to allow a comparison of the safety of Verkazia versus vehicle.
- The ‘All Periods cohort’ (n=273) including all patients who received NOVA22007 in VEKTIS or NOVATIVE at any point in time during the study including both evaluation and follow-up periods.

Therefore the safety database includes all patients who received at least one dose of CsA at any time during the 2 studies, and provides for the assessment of long-term safety.

In addition, two dose groups were identified:

- The high dose group includes patients from NOVATIVE and VEKTIS who received CsA 0.1% QID;

- The low dose group includes NOVATIVE patients who received CsA 0.05% QID and VEKTIS patients who received CsA 0.1% BID.

Safety evaluations consisted of reports of (ocular and systemic) adverse events (AEs), serious adverse events (SAEs), deaths, laboratory data including ciclosporinaemia, vital signs and ocular and external ocular examination (Best Corrected Distance Visual Acuity [BCDVA], IOP). Special safety topics included safety events possibly related to Verkazia, CsA systemic absorption and off label use.

Causality, intensity, seriousness, and outcome assessment were performed by the investigator for all AEs. AEs judged as possibly or probably related to the study drug were considered related to the treatment. Treatment emergent adverse events (TEAEs) were considered any AEs that occurred or worsened after treatment had started. TEAEs were summarised by system organ class (SOC), and Preferred term (PT) based on Medical Dictionary for Regulatory Activities (MedDRA), version 19.0.

In addition, the applicant made reference to Ikervis which consists of the same eye drop formulation and is approved for the treatment of severe keratitis in adult patients with dry eye disease. Clinical data from studies in patients with dry eye disease as well as the available post-marketing experience were provided, including the clinical trials (mainly the 2 Phase III studies SICCANOVE and SANSIKA) which formed the basis for approval of Ikervis in the EU in 2015 and comprised more than 700 patients. Notably, while Verkazia is a duplicate of Ikervis, the proposed dose regimen differs (2-4 times a day with Verkazia versus once a day with Ikervis) and the target populations deviate in age and diagnosis.

Patient exposure

In the combined VEKTIS and NOVATIVE studies, a total of 189 patients with VKC were treated with CsA of which 84 patients were treated with CsA 0.1% 4 drops/eye/day (QID) for at least 4 months. Of these, 49 patients completed the follow up period in VEKTIS (i.e. 12 months study period). A total of 44 patients received CsA 0.1% 2 drops/eye/day (BID) and completed the 4 months study period (Table 16).

Table 14 Safety Database for Verkazia (all doses)

Study	Indication	Duration Dose	Number of patients				
			0.05% 4 drops/day (n=39)	0.1% 2 drops/day (n=54)	0.1% 4 drops/day (n=96)	Vehicle (n=98)	Total CsA
NVG05L101 Phase II/III NOVATIVE (BAK)	Moderate to severe VKC	1 month (+ 3 month safety follow up)					
		Completed at M1	39	--	36	36	75
		Completed at M4	34	--	34	--	68
NVG09B113 Phase III VEKTIS (CKC)	Severe VKC	4 months (+ 8 month safety follow up)					
		Completed at M4	--	44	50	49	94
		Completed at M12	--	41	49	--	90
	TOTAL						
	TOTAL (at 1 month)		39	--	36	36	75
	TOTAL (at 4 months		34	44	84	49	162
	TOTAL (at 12 months)		--	41	49	--	90

Notably, Table 16 does not reflect the 48 patients in VEKTIS initially assigned to vehicle who, after completion of the 4-months evaluation phase, received either CsA 0.1% QID (22) or BID (26). In addition, in NOVATIVE, all vehicle patients who completed the 1-month evlauation period were assigned to one of the active treatment groups including 19 patients receiving CsA 0.05% QID and 17 patients receiving CsA 0.1% QID.

The mean exposure to Verkazia 0.1% QID and vehicle during the Double-Masked period (up to 4 months) was 76.0 days ± 43.3 and 74.1± 43.9 days, respectively. The mean exposure to Verkazia 0.1% QID in the All Periods cohort was 195.8 ± 116.6 days. Around 31% (n= 42/135) of patients were exposed to Verkazia 0.1% QID for more than 44 weeks (see Table 17 and Table 18).

For patient demographics and disease characteristics, see sections 2.5.2. and 2.5.3.

Table 15 Extent of Exposure – Double-Masked Cohort

Exposure	High dose regimen (N=96)	Low dose regimen (N=93)	Vehicle (N=98)
n	96	92	98
<= 1 week	1 (1.0%)	0	2 (2.0%)
>1 to 4 weeks	15 (15.6%)	11 (12.0%)	14 (14.3%)
>4 to 14 weeks	29 (30.2%)	38 (41.3%)	32 (32.7%)
>14 to 32 weeks	51 (53.1%)	43 (46.7%)	50 (51.0%)
>32 to 44 weeks	0	0	0
>44 to 52 weeks	0	0	0
>52 weeks	0	0	0
Number of days: Mean (SD)	76.0 (43.3)	71.2 (42.4)	74.1 (43.9)

Table 16 Extent of Exposure – All Periods Cohort

Exposure	High dose regimen (N=135)	Low dose regimen (N=138)
n	135	135
<= 1 week	5 (3.7%)	1 (0.7%)
>1 to 4 weeks	5 (3.7%)	2 (1.5%)
>4 to 14 weeks	20 (14.8%)	33 (24.4%)
>14 to 32 weeks	47 (34.8%)	54 (40.0%)
>32 to 44 weeks	15 (11.1%)	15 (11.1%)
>44 to 52 weeks	42 (31.1%)	29 (21.5%)
>52 weeks	1 (0.7%)	1 (0.7%)
Number of days: Mean (SD)	195.8 (116.6)	173.3 (107.3)

Adverse events

In the Double Masked Cohort

A total of 105 (36.9%) patients reported TEAEs. Across the treatment groups, the percentages of patients with a TEAE were similar with 37.5% (36/96) for the high dose group, 34.4% (32/93) for the low dose group and 37.8% (37/98) for the vehicle group. The percentage of patients with a drug related TEAE was 21.9% (21/96) for the high dose regimen, 17.2% (16/93) for the low dose regimen and 17.3% (17/98) for the vehicle group (see Table 19).

Table 17 Overview of AEs (Double-Masked Cohort)

		High dose regimen (N=96)	Low dose regimen (N=93)	Vehicle (N=98)
All TEAEs		36 (37.5%)	32 (34.4%)	37 (37.8%)
Drug-related TEAEs		21 (21.9%)	16 (17.2%)	17 (17.3%)
Severity of TEAEs	Mild	16 (16.7%)	24 (25.8%)	13 (13.3%)
	Moderate	14 (14.6%)	2 (2.2%)	18 (18.4%)
	Severe	6 (6.3%)	6 (6.5%)	6 (6.1%)
Severity of Drug-related TEAEs	Mild	11 (11.5%)	13 (14.0%)	5 (5.1%)
	Moderate	8 (8.3%)	1 (1.1%)	9 (9.2%)
	Severe	2 (2.1%)	2 (2.2%)	3 (3.1%)
Death		0	0	0
SAE		2 (2.1%)	1 (1.1%)	0
Drug-related SAE		0	0	0
Discontinuation due to TEAEs		5 (5.2%)	0	10 (10.2%)
Discontinuation due to Drug-related TEAEs		3 (3.1%)	0	5 (5.1%)

Note: A patient is counted only once in his/her maximal severity.

The most common TEAEs occurred mainly in the two following MedDRA SOCs: 'Eye disorders' and 'General disorders and administration site conditions'. The observed proportion of 'Eye disorders' TEAEs was higher in the high dose group (17/96; 17.7%) and in the vehicle group (18/98; 18.4%) as

compared to the low dose group (6/93; 6.5%). The proportion of ‘General disorders and administration site conditions’ TEAEs was higher in the low dose group (18/93; 19.4%) and in the high dose group (14/96; 14.6%) as compared to the vehicle group (8/98; 8.2%).

Table 18 Most frequent TEAEs – Double Masked Cohort (4 Months)

System Organ Class Preferred Term	High dose regimen (N=96)	Low dose regimen (N=93)	Vehicle (N=98)
Eye disorders	17 (17.7%)	6 (6.5%)	18 (18.4%)
Ulcerative keratitis	4 (4.2%)	3 (3.2%)	6 (6.1%)
Ocular hyperaemia	3 (3.1%)	2 (2.2%)	2 (2.0%)
Allergic keratitis	2 (2.1%)	1 (1.1%)	3 (3.1%)
Visual acuity reduced	3 (3.1%)	0	2 (2.0%)
Corneal leukoma	2 (2.1%)	0	1 (1.0%)
Eye irritation	1 (1.0%)	0	1 (1.0%)
Eye pain	1 (1.0%)	1 (1.1%)	0
Foreign body sensation in eyes	2 (2.1%)	0	0
Blepharitis	1 (1.0%)	0	0
Blepharospasm	1 (1.0%)	0	0
Cataract subcapsular	0	0	1 (1.0%)
Chalazion	1 (1.0%)	0	0
Corneal deposits	0	0	1 (1.0%)
Corneal disorder	0	0	1 (1.0%)
Erythema of eyelid	1 (1.0%)	0	0
Eyelid erosion	1 (1.0%)	0	0
Eyelid oedema	0	0	1 (1.0%)
General disorders and administration site conditions	14 (14.6%)	18 (19.4%)	8 (8.2%)
Instillation site pain	9 (9.4%)	7 (7.5%)	4 (4.1%)
Instillation site pruritus	6 (6.3%)	7 (7.5%)	3 (3.1%)
Instillation site erythema	1 (1.0%)	1 (1.1%)	2 (2.0%)
Pyrexia	0	1 (1.1%)	2 (2.0%)
Drug intolerance	0	2 (2.2%)	0
Application site discharge	0	0	1 (1.0%)
Application site swelling	0	1 (1.1%)	0
Hyperthermia	0	1 (1.1%)	0
Instillation site irritation	0	1 (1.1%)	0
Infections and infestations	4 (4.2%)	10 (10.8%)	4 (4.1%)
Nasopharyngitis	0	3 (3.2%)	1 (1.0%)
Hordeolum	0	1 (1.1%)	1 (1.0%)
Otitis externa	0	2 (2.2%)	0
Pharyngitis	2 (2.1%)	0	0
Bronchiolitis	0	0	1 (1.0%)
Conjunctivitis	0	0	1 (1.0%)
Gastroenteritis	0	1 (1.1%)	0
Gastroenteritis viral	0	1 (1.1%)	0
Parasitic gastroenteritis	0	1 (1.1%)	0

System Organ Class Preferred Term	High dose regimen (N=96)	Low dose regimen (N=93)	Vehicle (N=98)
Rhinitis	0	0	1 (1.0%)
Tonsillitis	0	1 (1.1%)	0
Upper respiratory tract infection	1 (1.0%)	0	0
Varicella	1 (1.0%)	0	0
Respiratory, thoracic and mediastinal disorders	4 (4.2%)	4 (4.3%)	5 (5.1%)
Oropharyngeal pain	1 (1.0%)	2 (2.2%)	1 (1.0%)
Cough	2 (2.1%)	0	1 (1.0%)
Asthma	0	1 (1.1%)	1 (1.0%)
Allergic respiratory disease	1 (1.0%)	0	0
Epistaxis	0	1 (1.1%)	0
Rhinorrhoea	1 (1.0%)	0	0
Sneezing	0	0	1 (1.0%)
Throat tightness	0	0	1 (1.0%)
Skin and subcutaneous tissue disorders	3 (3.1%)	0	5 (5.1%)
Urticaria	0	0	2 (2.0%)
Acne	1 (1.0%)	0	0
Dermatitis allergic	0	0	1 (1.0%)
Eczema	1 (1.0%)	0	0
Papule	1 (1.0%)	0	0
Rash	0	0	1 (1.0%)
Skin irritation	0	0	1 (1.0%)
Injury, poisoning and procedural complications	2 (2.1%)	2 (2.2%)	1 (1.0%)
Accident	1 (1.0%)	0	0
Eyelid injury	0	1 (1.1%)	0
Face injury	0	0	1 (1.0%)
Head injury	0	1 (1.1%)	0
Tibia fracture	1 (1.0%)	0	0
Nervous system disorders	4 (4.2%)	0	1 (1.0%)
Headache	4 (4.2%)	0	1 (1.0%)
Gastrointestinal disorders	2 (2.1%)	0	2 (2.0%)
Aphthous ulcer	1 (1.0%)	0	1 (1.0%)
Vomiting	1 (1.0%)	0	1 (1.0%)
Nausea	0	0	1 (1.0%)
Investigations	0	0	2 (2.0%)
Aspartate aminotransferase increased	0	0	1 (1.0%)
Blood creatine phosphokinase increased	0	0	1 (1.0%)

System Organ Class Preferred Term	High dose regimen (N=96)	Low dose regimen (N=93)	Vehicle (N=98)
Blood lactate dehydrogenase increased	0	0	1 (1.0%)
Intraocular pressure increased	0	0	1 (1.0%)
Protein total increased	0	0	1 (1.0%)
Ear and labyrinth disorders	0	0	1 (1.0%)
Ear pain	0	0	1 (1.0%)
Immune system disorders	0	1 (1.1%)	0
Seasonal allergy	0	1 (1.1%)	0
Musculoskeletal and connective tissue disorders	1 (1.0%)	0	0
Pain in extremity	1 (1.0%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0%)	0	0
Skin papilloma	1 (1.0%)	0	0

Note: If a subject has more than one AE within PT the subject will be counted only once.
Note: MedDRA Version 19.0.

Ocular TEAEs were reported in similar proportions of patients in the 3 treatment groups, with 29.2% in the high dose group, 24.7% in the low dose group and 26.5% with vehicle. Ocular TEAEs were considered to be treatment related in a higher proportion of patients (20.8%) treated with the high dose regimen, than in those receiving the low dose (17.2%) or vehicle (14.3%).

Systemic TEAEs were reported in a similar proportion in the 3 treatment groups (14.6% [14/96], 15.1% [14/93] and 15.3% [15/98], for the CsA high dose regimen, low dose regimen and vehicle, respectively). Of these, only 2.1% (n=2/96) were considered drug related in the high dose group and 3.1% (n=3/98) with vehicle. No systemic drug-related TEAEs were reported in the low dose group. In the high dose group, the AEs considered related to treatment were headache and cough in 1 patient and rhinorrhoea in 1 patient (1% each). No serious drug related systemic TEAE was reported.

The most frequent AEs observed were instillation site pain [9 (9.4%) cases in the high dose group, 7 (7.5%) cases in the low dose group, and 4 (4.1%) cases in the vehicle group], instillation site pruritus [6 (6.3%) cases in the high dose group, 7 (7.5%) cases in the low dose group, and 3 (3.1%) cases in the vehicle group] and ulcerative keratitis [4 (4.2%) cases in the high dose group, 3 (3.2%) cases in the low dose group, and 6 (6.1%) cases in the vehicle group].

Drug related TEAEs were mainly ocular AEs. The most frequently reported TEAEs assessed by the investigator as having at least a possible relationship to treatment were instillation site pain (9 [9.4%], 7 [7.5%] and 4 [4.1%] in the high dose, in the low dose and in the vehicle groups, respectively) and instillation site pruritus (5 [5.2%], 7 [7.5%] and 3 [3.1%] in the high dose, in the low dose and in the vehicle groups, respectively). Ulcerative keratitis was considered drug-related in 2 cases (3.0%) in the vehicle group.

In the All Periods Cohort

A total of 122 (44.7%) patients had a TEAE. Across the treatment group, the percentage of patients with a drug related TEAE was 23.0% (31/135) with the high dose regimen and 21.7% (30/138) with the low dose regimen.

The most common TEAEs experienced by patients occurred mainly in the two following MedDRA SOCs: 'Eye disorders' and 'General disorders and administration site conditions'. The observed proportion of 'Eye disorders' was higher in the high dose group (26/135; 19.3%) as compared to the low dose group (16/138; 11.6%). The proportion of 'General disorders and administration site conditions' was higher in the low dose group (29/138; 21.0%) as compared to the high dose group (24/135; 17.8%).

Ocular TEAEs were reported in a similar proportion of patients treated with the high dose (44/135; 32.6%) and the low dose (43/138; 31.2%). Ocular TEAEs were considered to be treatment related in 22.2% (30/135) of patients treated with the high dose and 21.7% (30/138) in the low dose group. The most frequently reported ocular TEAEs assessed by the investigator as having at least a possible relationship to treatment were instillation site pain [15 (11.1%) cases in the high dose group, and 11 (8.0%) cases in the low dose group], instillation site pruritus [7 (5.2%) cases in the high dose group, and 11 (8.0%) cases in the low dose group], ocular hyperaemia [3 (2.2%) cases in the high dose group, and 2 (1.4%) cases in the low dose group] and visual acuity decreased [3 (2.2%) cases in the high dose group, and 1 (0.7%) cases in the low dose group]. Ulcerative keratitis was reported for 4 (3.0%) and 5 (3.6%) patients in the high dose and the low dose groups, respectively, but was only considered drug-related in 1 case (0.7%) in the low dose group. Furthermore, the following TEAEs were considered drug-related in at least one case in an active treatment arm: eye irritation (1 case each in the active groups), Instillation site foreign body sensation (1 case in the low dosed group) and Instillation site lacrimation (1 case each in the active groups).

Ocular infections were reported in 3 cases. Two cases (one of conjunctivitis viral and one of folliculitis) occurred with the high dose regimen, which were moderate in intensity, and one mild case of hordeolum with the low dose regimen was reported. They were all considered not related to study medication by the investigators.

Systemic TEAEs were reported in a similar proportion in the treatment groups (23.0% [31/135] and 18.8% [26/138] for the high dose and the low dose groups, respectively). Only 2 cases, all in the high dose regimen (1.5%), were considered drug related. There were only 2 drug related systemic TEAEs: One case of headache (0.7%) and one case of rhinorrhoea (0.7%), both reported in the high dose group. No serious drug related systemic TEAE was reported.

Studies in adult patients with dry eye disease

The safety for of CsA eye drops in the treatment of adult patients with dry eye disease has previously been reviewed during the initial marketing authorisation application for Ikervis, including pooled data analysis such as 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 CsA 0.1%, 1 drop once daily and (ii) a Phase IIb study(ORA), taking into account only patients (45 patients) exposed to CsA 0.1%, 1 drop once daily.

The most frequently reported ocular TEAEs assessed by the investigator as having at least a possible relationship to CsA treatment in the 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.

Of these, the following adverse reactions which did not occur in VKC paediatric patients were judged to potentially also be relevant for the latter population:

- vision blurred, erythema of eyelid, and eyelid oedema (common);

- conjunctival oedema, keratitis bacterial, herpes zoster ophthalmic (uncommon).

Serious adverse event / deaths / other significant events

No death was reported during the development programme for Verkazia.

In the Double Masked Cohort, 2 patients (2.1%) reported a SAE in high dose group (ulcerative keratitis and tibia fracture), 1 in the low dose group (head injury), and none in the vehicle group. All these SAEs were judged not drug related.

In the All Periods Cohort, 3 patients (2.2%) reported a SAE in the high dose group (ulcerative keratitis, tibia fracture and phimosis), and 2 (2.9%) in low dose group (head injury and asthma). These SAEs were judged not drug related.

Laboratory findings

Ciclosporinaemia

CsA blood concentrations were measures in both the NOVATIVE and the VEKTIS study (see section 2.4.2. for details). For most patients, no or negligible systemic exposure was detected. In VEKTIS (which provided the largest blood sampling) 14/48 (29.2%) patients in the high dose group (CsA 0.1 QID) and 5/41 (12.2%) patients in the low dose group (CsA 0.1% BID) had quantifiable CsA blood levels at Month 4 with values up to 0.670 ng/ml in the high dose group and 0.336 ng/ml in the low dose group. The same pattern was observed when analysing the data separately for children and adolescents (from 4-11; and above 11) showing a systemic passage of CsA in some patients and more specifically for those receiving the high dose. At Month 12, there was still a number of patients (12/68 in the high dose group vs. 5/61 in the low dose group) with quantifiable CsA in the blood, although to a lesser extent when compared to Month 4, but no accumulation occurred.

Transaminases (ALT, AST) and Creatinine

In VEKTIS, overall, there were no clinically relevant changes in alanine aminotransferase, aspartate aminotransferase or creatinine over the 4-month randomised period or the 8-month follow-up period in either treatment group. There was no difference between children and adolescents.

In NOVATIVE, the majority of laboratory values were within the normal ranges. In very few instances, out of range values were recorded in all treatment groups. However, none of these values were judged clinically relevant. No trends were observed.

Vital signs

Vital signs were only recorded in VEKTIS. Overall, there were no clinically relevant changes in blood pressure (systolic, diastolic), pulse rate or respiratory rate over the 4-month randomised period or the 8-month follow-up period in either treatment group. There was no difference between the child and adolescent age group.

Best Corrected Distance Visual Acuity (BCDVA)

In VEKTIS, during the 4-Month Randomised Period measurement of BCDVA showed an improvement over the 4-month randomised period in all treatment groups, most prominent in the high dose group with a mean change from baseline to Month 4/Early termination of -0.135 (SD: 0.220), followed by the low dose (-0.091 [SD: 0.257]) and vehicle group (-0.097 [SD: 0.210]).

In NOVATIVE, mean BCDVA values were similar for all treatment groups at Baseline and at all subsequent time points.

Measurement of IOP

In VEKTIS, during the 4-Month randomised period stable IOP was noted for all treatment groups with a mean change from baseline to Month 4/Early termination of -0.4 mmHg (SD: 2.7) in the high dose group, -0.2 mmHg (SD: 2.4) in the low dose group, and 0.1 mmHg (SD: 2.4) in the vehicle group. Similarly during the follow-up period, IOP remained overall stable with mean changes from baseline (Month 4) to Month 12/Early termination of 0.3 mmHg (SD: 2.1) in the high dose total group and 0.0 mmHg (SD: 2.5) in the low dose total group.

Safety in special populations

Based on the available clinical data, there was no evidence of any intrinsic factor e.g. age, sex, race affecting the safety of Verkazia.

Comparative safety analyses by age groups (4-7 years, 8-11 years, 12-17 years) showed a trend for an increase in the incidence rate of TEAEs in the youngest age group compared to older paediatric patients. However, no firm conclusions could be drawn for the impact of age on the occurrence of TEAEs (ocular and/or non-ocular), nor their severity of impact on treatment (dis-)continuation due to the size of the study.

No specific evaluation of extrinsic factors was conducted in the development program for Verkazia.

Studies in animals conducted with systemic CsA have shown reproductive toxicity at high dosages. The potential risk for humans is unknown. No clinical study has been conducted in pregnant or lactating women in support of this application. The clinical studies conducted with Verkazia excluded patients at risk of pregnancy, and patients who were pregnant or breast-feeding and there were no known pregnancies in the clinical studies. One pregnancy case was reported during the compassionate use of Ikervis in France, with no safety issue reported during the follow up of the pregnancy or at the delivery. The new-born did not experience any AE. Also, one breastfeeding case was reported since the authorisation of Ikervis in March 2015, and the child did not experience any adverse event.

Safety related to drug-drug interactions and other interactions

No specific studies of potential drug interactions were performed given the local route of administration and low systemic exposure to CsA observed. This was considered acceptable by the CHMP. The CHMP furthermore welcomed that the applicant is already conducting a non-clinical drug-drug interaction study to further explore the interaction potential of CsA eye drops at the transporter level as well as at the cellular level.

Co administration of CsA 0.1% with corticosteroids occurred during the VEKTIS study [high dose (32.1%) and low dose (31.5%)] with no safety issues arising.

Discontinuation due to AEs

In the Double Masked Cohort, in total 15 (5.2%) patients discontinued from the study during the double masked period due to an AE and 8 (2.8%) of these patients discontinued for a drug related TEAE. Of these 8 patients, 3 (3.1%) patients discontinued due to a drug related AE in the high dose group. The incidence was slightly higher in the vehicle group (5; 5.1%). Most of these AEs were ocular AEs (ulcerative keratitis, allergic keratitis, eye irritation, eye pain, lacrimation, visual acuity reduced).

In the All Periods Cohort, 11/371 (4.0%) patients discontinued due to a TEAE and seven (2.5%) patients discontinued due to a drug related TEAE. Most of these AEs were ocular AE.

Post marketing experience

Post-marketing data were presented for Ikervis, which was authorised in the EU via Commission Decision in March 2015. Since the beginning of the marketing of Ikervis (i.e., 8 June 2015) until 30 September 2016, a total of 73,322 monthly doses have been sold. The cumulative patient exposure from post-marketing experience was estimated at 6,110 patient years. One hundred and seven (107) non-serious Adverse Drug Reactions (ADRs) related to Ikervis were derived from spontaneous reporting sources. Seventy (70) ADRs were under the SOC of Eye disorders, eye irritation (16) being the most frequent event followed by eye pain (12) and ocular hypaeremia (10). A total of 24 serious ADRs occurred (aspergillus infection, atypical mycobacterial infection, cytomegalovirus infection, pneumonia, malignant neoplasm of conjunctiva (2), condition aggravated (2), basal cell carcinoma, dizziness (2), headache, eye irritation, vision blurred, photophobia, ulcerative keratitis, cardiac flutter, hypertensive crisis, peripheral coldness, obliterative bronchiolitis, pneumothorax, lip swelling, renal impairment and chest pain).

Since Ikervis launch in France, two valid and two invalid cases with MedDRA PTs ‘malignant neoplasm of conjunctiva’ and ‘condition aggravated’ relating to squamous carcinoma conjunctival have been spontaneously reported. All reports were received from a single source and are related. The reports were lacking sufficient information for a full medical assessment.

2.6.1. Discussion on clinical safety

The main basis for the safety evaluation of Verkazia was the pooled data from the 2 Phase 3 trials VEKTIS and NOVATIVE. Together, these 2 studies contributed data from 189 VKC patients who received treatment with CsA 0.1%. Two safety cohorts were used, the 'Double masked study cohort' including all patients from the double masked period of the VEKTIS and NOVATIVE study (i.e. up to 4 months) and the 'All Periods cohort' including all patients who received CsA 0.1% in VEKTIS or NOVATIVE at any point in time including the follow-up periods (i.e up to 12 months). These two cohorts included data from 84 and 49 patients, respectively, who received CsA 0.1% QID for at least 4 and 12 months. Furthermore, supportive data were available from previous experience of the use of CsA 0.1% (Ikervis) in adult patients with dry eye disease.

Overall, the applicant's approach for the safety evaluation was considered acceptable.

Due to the rarity of the disease, the safety database in the target population was limited in size. The small number of exposed VKC patients, in particular those receiving CsA at the strength and dose intended for commercial use (0.1% QID) precluded realistic frequency estimations and the detection of rare events. Nevertheless, the data from VEKTIS and NOVATIVE suggested that Verkazia has generally been well tolerated. Only very few SAEs were reported (5 cases) in patients receiving CsA eye drops and all cases were judged unrelated to treatment. Only 3 patients receiving CsA discontinued due to a drug related AE (all in the 0.1% QID group). In fact, more patients in the vehicle arm (5) discontinued for this reason.

The most common TEAEs reported were ocular and belonged to the MedDRA SOCs *General disorders and administration site conditions* and *Eye disorders*. Within these SOCs, reports for instillation site reactions were considered synonymous to eye reactions. When grouping related terms together, the most common adverse reactions observed in the clinical development program were eye pain (11%) and eye pruritus (9%) which were usually transitory and occurred during instillation.

Similarly, TEAEs judged to be at least possibly related to treatment were mainly ocular AEs. In the Double masked cohort, ocular TEAEs were considered to be treatment related in a higher proportion of patients (20.8%) treated with the high dose regimen, than in those receiving the low dose (17.2%) or vehicle (14.3%). In the All Periods cohort, which included data up to 12 months, ocular TEAEs were considered to be treatment related in 22.2% of patients treated with CsA 0.1% QID and 21.7% in the CsA 0.1% BID group. The most frequently reported ocular TEAEs assessed by the investigator as having at least a possible relationship to treatment were instillation site pain with 15 (11.1%) cases in the high dose group, and 11 (8.0%) cases in the low dose group, instillation site pruritus with 7 (5.2%) cases in the high dose group, and 11 (8.0%) cases in the low dose group, and ocular hyperaemia with 3 (2.2%) cases in the high dose group, and 2 (1.4%) cases in the low dose group. Furthermore, the following TEAEs were considered drug-related in at least one case in an active treatment arm: eye irritation (1 case each in the active groups), instillation site foreign body sensation (1 case in the low dosed group) and instillation site lacrimation (1 case each in the active groups).

For eye/instillation site pain and eye/instillation site pruritus, reporting rates were higher with active treatment compared to vehicle (Double Blind Cohort): 9/96 (9.4%), 7/93 (7.5%), and 4/98 (4.1%) of the patients in the CsA 0.1% high dose regimen, CsA 0.1% low dose regimen and vehicle group, respectively, reported instillation site pain and 6/96 (6.3%), 7/93 (7.5%), and 3/98 (3.1%) of the patients in the CsA 0.1% high dose regimen, CsA 0.1% low dose regimen and vehicle group, respectively, reported instillation site pruritus.

Furthermore, blepharitis was reported in 2 cases in the high dose group and ocular discomfort was observed in 4 cases with CsA treatment (3 cases in the high dose group and 1 case in the low dose

group) in the All Exposed cohort. No such cases were reported with vehicle. While both types of events may be related to the underlying disease, the CHMP was of the view that a causal relation to CsA could not be excluded.

No relevant differences were apparent between the high and the low dose groups with regards to safety. In the All Periods cohort, in both groups, a similar percentage of patients reported drug related TEAEs (23.0% in the high dose group and 21.7% in the low dose group) and ocular TEAEs (32.6% in the high dose group and 31.2% in the low dose group).

Given the immunosuppressive properties of CsA, there is a risk of local adverse effects such as infections or malignancies in particular when using CsA eye drops over prolonged periods of time as could be the case in VKC patients. Overall, 3 cases of ocular infections were observed during the clinical trials programme of Verkazia. Two moderate cases (one of conjunctivitis viral and one of folliculitis) occurred with the high dose regimen, and one mild case of hordeolum with the low dose regimen was reported. All of these cases were considered unrelated to treatment. No cases of peri-ocular skin cancer, conjunctival or corneal neoplasia were observed in VEKTIS or NOVATIVE. However, few cases of malignancies (conjunctival carcinoma) have been reported for Ikervis in the post-marketing setting, although they lacked sufficient information to allow a full medical assessment.

Peri-ocular skin cancer, conjunctival or corneal neoplasia as well as development and exacerbation of ocular and peri-ocular infections are considered important potential risks in the RMP of Verkazia. A warning statement was included in SmPC section 4.4 advising regular monitoring of the eye when Verkazia is used long term. The SmPC also advises that Verkazia should not be used in patients with active or suspected ocular or peri-ocular infection and that concomitant use of corticosteroid eye drops may potentiate the immunosuppressive effect. Together, these measures were considered sufficient to mitigate the potential risks related to a reduced local immune response. Finally, to further evaluate the potential risk of periocular skin cancer, conjunctival or corneal neoplasia in the paediatric population, a case control study linked to existing cancer registries is foreseen (category 3 in the RMP) depending on the outcome of a feasibility study to understand the data sources and analytic methods available to quantify these risks in the target population. Furthermore, a targeted follow-up questionnaire will be used to collect data systemically on all reports of cases of periocular skin cancer, conjunctival or corneal neoplasia.

Ocular AEs identified during the clinical development of Verkazia were broadly consistent with the safety profile of Ikervis which consists of the same eye drop formulation and is approved for use in adult patients with dry eye disease and severe keratitis, 1 drop a day in the evening. The safety database for patients with dry eye disease was much larger compared to the one of Verkazia in VKC patients and some of the adverse reactions identified herein were considered to be also relevant for VKC including vision blurred, erythema of eyelid, and eyelid oedema (common) as well as conjunctival oedema, keratitis bacterial, and herpes zoster ophthalmic (uncommon).

Systemic TEAEs were reported in a similar proportion in the 3 treatment groups. Two patients receiving CsA 0.1% QID has systemic TEAEs considered treatment related, including one patient reporting headache and cough. Overall, both of these TEAEs were reported more frequently with active treatment than with vehicle.

Furthermore, reports of upper respiratory tract infection, nasopharyngitis, pharyngitis, tonsillitis, laryngitis, rhinitis, oropharyngeal pain and rhinorrhoea were received. When summarising these events under a joint term of upper respiratory tract infection, the incidence rate was slightly higher in the CsA groups (5.8%) compared to the vehicle group (3.1%) at Month 4. A causal relation to CsA could not be ruled out based on its immunosuppressive action and the fact that it is absorbed after instillation through the nasolacrimal duct (albeit without resulting in significant systemic exposure). Therefore, upper respiratory tract infection was included as a common adverse reaction in SmPC section 4.8.

Ciclosporinaemia occurred in nearly 30% of the patients receiving CsA 0.1% QID (see 2.4.2. for details). This was however not considered to represent a safety concern as the observed blood levels were substantially lower compared to CsA levels reached in case of systemic immunosuppression.

No interaction studies have been performed with Verkazia. Co administration of CsA 0.1% with corticosteroids occurred during the VEKTIS study [high dose (32.1%) and low dose (31.5%)] with no specific safety issues arising.

Furthermore, use in pregnant and breast-feeding women was not studied. Reports on one pregnancy case and one case of use of Ikervis during breastfeeding revealed no adverse effects. However, studies in animals with systemic CsA have shown reproductive toxicity at high dosages. Therefore, despite the low systemic exposure at therapeutic doses, Verkazia is not recommended in women of childbearing potential not using effective contraception and use during pregnancy and in lactating women is only recommended if the benefits outweigh the risks. Use in pregnant or lactating women is furthermore considered missing information in the RMP and will be monitored post-approval.

Since younger children could be more sensitive to adverse effects of CsA eye drops compared to older ones, the applicant presented comparative safety data for different age groups (4-7, 8-11, 12-17 years old). While there was a trend toward an increase of patients experiencing TEAEs in the youngest age group for the high dose regimen, the small sample size did not allow drawing form conclusions on the impact of age on TEAE occurrence, severity, frequency and treatment discontinuation.

The CHMP also noted that patients wearing contact lenses have not been studied. Therefore, the use of Verkazia with contact lenses is not recommended.

Finally, given that only few patient data were available for an exposure to CsA 0.1% QID up to 12 months, long-term safety was considered missing information in the RMP. Further data are expected to be collected by means of routine Pharmacovigilance including periodic safety update reports and a targeted follow-up questionnaire to collect data systemically on all cases of periocular skin cancer, conjunctival or corneal neoplasia.

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 Verkazia in the treatment of severe VKC in children from 4 years of age and adolescents. In general, Verkazia was well tolerated with mostly ocular AEs such as eye pain and eye pruritus which usually occurred during instillation and resolved shortly after. Uncertainties remained in relation to the risk of infections and malignancies as a result of a local suppression of the immune response in particular when Verkazia is used over prolonged periods of time and because of the limited amount of (long-term) safety data with the dose regimen proposed for clinical practice (CsA 0.1%, QID). The feasibility to perform a case-control study to generate additional data post-marketing will be explored by the applicant as a requirement in the RMP.

2.7. Risk Management Plan

Safety concerns

Table 19 Summary of the safety concerns

SAFETY CONCERNS RELATING TO THE ACTIVE SUBSTANCE (i.e. relevant to IKERVIS and VERKAZIA)	
Important Identified risks	None
Important potential risk	- 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.
SAFETY CONCERNS RELATING TO THE PEDIATRIC TARGET POPULATION (i.e. relevant only to VERKAZIA)	
Missing information	- Long-term safety

Pharmacovigilance plan

Table 20 On-going and planned additional PhV studies/activities in the PV plan

Study	Objectives	Safety concerns addressed	Status	Milestones
VERKAZIA PASS (Category 3) A feasibility study for a case-control study linked to existing cancer registries	To understand the data sources and analytic methods available to quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with VERKAZIA for VKC.	Risk of malignancies	Planned	Q4-2017: Submission of the protocol for the feasibility study for PRAC review / endorsement within 3 months from the EC decision on VERKAZIA MA Q2-2019: Submission of the study report
A Phase IV case control study linked to existing cancer registries	To quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated			The conduct of this study is conditional, depending on the outcome of the feasibility study Q1-2020:

	with VERKAZIA for VKC.			Submission of the protocol for PRAC review/ endorsement -Submission of the study report within 6 months from the end of the study

Risk minimisation measures

Table 21 Summary of the risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks N/A		
Important potential risks		
Hypersensitivity (angioedema)	Wording in EU SmPC (4.3)	N/A
Development/exacerbation of ocular/peri-ocular infection	Wording in EU SmPC (4.3)	N/A
Peri-ocular skin cancer, conjunctival or corneal neoplasia	Wording in EU SmPC (4.4)	N/A
Missing information		
Use in pregnancy and lactation	Wording in EU SmPC (4.6)	N/A
VERKAZIA: Long-term safety	Wording in EU SmPC (4.2 and 4.4)	N/A

Conclusion

The CHMP and PRAC considered that the RMP version 6.0 (dated 27 June 2017) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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 following information will be displayed: Invented name, strength, INN (English only), EXP and Lot.

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 required 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. Therefore, by requesting an exemption to translate the INN, the label of this immediate single-dose container will be in English only. 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

3.1.1. Disease or condition

Verkazia is intended for the treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.

VKC is a rare ocular allergic disease characterised by an inflammation of the conjunctivitis with corneal involvement, mainly affecting boys from the age of 5 to 12 years and commonly resolving at puberty. It usually affects both eyes and appears mainly seasonally but can also be perennial, chronic and/or with acute exacerbations. Two phenotypes exist; the palpebral/tarsal form, which is characterised by papillae at the upper tarsal conjunctiva, and the limbal form with thickening and opacification of the limbal conjunctiva and possibly corneal neovascularisation, but there are also mixed forms. Disease severity is defined based on clinical signs and symptoms of ocular surface inflammation. Typical symptoms include photophobia, burning, pruritus, mucous discharge, irritation and foreign body sensation.

The aim of therapy is to alleviate symptoms and in severe cases, to prevent sight threatening complications including corneal ulceration, scarring, opacities, and keratoconus.

3.1.2. Available therapies and unmet medical need

The management of VKC involves a stepwise approach based on disease severity. Cool compresses, saline rinses and preservative-free artificial tears can be used at all stages to improve symptoms. Among topical medications, antihistamines and mast cell stabilisers, as well as other agent such as acetylcysteine, mitomycin-C and ketorolac are used. In more severe disease, corticosteroids are very effective, particularly in quieting disease exacerbations. However, long-term administration of corticosteroids is associated with a high risk of adverse reaction such as cataract, glaucoma, and infection, which limits their use in particular in the paediatric population. Use of antihistamine/mast cell stabilisers as maintenance therapy and then pulse therapy with topical steroids during disease exacerbations is a common practice. Finally, hospital-compounded preparations of 0.5% to 2% CsA ophthalmic emulsion in olive or castor oil have been used for decades in moderate to severe forms of VKC.

Given the possible irreversible sight-threatening character of severe forms of VKC in the paediatric population, and in light of the safety concerns with long-term use of corticosteroids, there is a need for treatment options with demonstrated efficacy in this setting and an acceptable safety profile.

3.1.3. Main clinical studies

The pivotal study supporting this application was a multicentre, randomised, double-blind, double-masked, vehicle controlled Phase III trial (VEKTIS) investigating the efficacy and safety of CsA 0.1% eye drops given either 2 times (BID) or 4 times daily (QID) to children and adolescents with severe VKC (grade 3 or 4 of Bonini scale) including corneal involvement (grade 4 or 5 on the modified Oxford scale). A total of 168 patients were included in the efficacy analyses including 127 children (75.6%) and 41 adolescents (24.4%). The double-blind evaluation phase was 4 months followed by an 8-months extension period in which patients were allowed to receive active treatment, resulting in a total observation period of 12 months.

3.2. Favourable effects

After 4 months of treatment, the penalty-adjusted corneal fluorescence staining (CFS) score, which was the primary endpoint in VEKTIS, increased in both active groups to a larger extent than with vehicle (difference in the LS mean vs. vehicle was 0.76 [95% CI: 0.26, 1.27] and 0.67 [95% CI: 0.16, 1.18] for the high and the low dose group, respectively) and the difference was statistically significant (p=0.007 and p=0.010). Furthermore, a larger proportion of patients in the high and low dose groups (57.1% and 61.1%) compared to vehicle (34.5%) fulfilled the criteria of CFS responders at Month 2, 3, and 4, defined as patients with a CFS score ≤ 50% of the baseline CFS, who did not withdraw from the study for a reason possibly due to treatment, not requiring rescue medication and having no ulcers. When including Month 1 into the analysis (originally omitted as it was hypothesised that many patients would take rescue medication during the first days of treatment and therefore would have been considered non-responders), the difference between active treatment and vehicle remained with a responder rate of 55.4%, 50.0% and 27.6% in the high dose group, low dose group and vehicle, respectively (p=0.005 and 0.010). The corresponding odds ratios (95% CI) were 3.279 (1.501, 7.163) and 2.798 (1.260, 6.211) for the high and the low dose group, respectively.

Furthermore, an improvement in subjective symptoms, including photophobia, tearing, itching and mucous discharge, as measured using a 100mm visual analogue scale (VAS) score was observed over time in all treatment groups. Compared to vehicle, a greater change in the VAS score was observed for both active treatment groups at Month 4; the difference in the LS mean change of the average symptom score was -19.4mm (p<0.001) and -8.4mm (p=0.103) for the high dose and the low dose regimen, respectively. The results by symptom were consistent with the overall symptom score showing a greater improvement for each of the individual symptom scores with active treatment compared to vehicle. The effect size at Month 4 for each of the symptoms and the overall symptom score was generally within the range of 8-10mm for the low dose and 14-20mm for the high dose.

The analysis of the use of rescue medication (dexamethasone 0.1% eye drops) also supported superiority of CsA 0.1% QID and BID over vehicle. Rescue medication was used by 32.1% (18/56) of the patients in the high dose group, 31.5% (17/54) in the low dose group, and 53.4% (31/58) in the vehicle group. The difference versus vehicle in the mean number of rescue medication courses per months was statistically significant for the high dose group (p=0.010) and close to significance for the low dose group (p=0.055).

Finally, data gathered during the 8 months follow-up period of the study suggested maintenance of the treatment effect in patients who continued active treatment after the initial 4 months evaluation period.

3.3. Uncertainties and limitations about favourable effects

The main evidence for efficacy of Verkazia in the treatment of severe VKC was based on a small number of patients including 56 and 54 patients being treated in VEKTIS with CsA 0.1% QID and BID, respectively. While justified due to the rarity of the disease, the small study size made the interpretation of the results difficult at times, e.g. in case of subgroup analyses. Furthermore, efficacy and safety of Verkazia have not been studied beyond 12 months.

The distribution of patients (75% children aged 4 to ≤11 years and 25% adolescents) was generally in line with the clinical presentation of the disease which usually resolves after puberty. However, there are cases where the disease continues into adulthood. The lack of data in adult patients has been reflected in the SmPC of Verkazia.

In VEKTIS, the primary efficacy endpoint was a composite score based on the change from baseline in keratitis/ocular surface damage measured as CFS adjusted by penalties for the use of rescue medication and the occurrence of corneal ulcers. Analyses evaluating the relative contribution of each of the subcomponents of the composite endpoint showed that the CFS score was the main driver of the magnitude of the observed treatment effect, with rescue medication contributing to a lesser degree. Corneal ulcers hardly occurred within the 4 months evaluation period of the study and no difference between active and vehicle groups was seen. Thus, no conclusion on the efficacy of Vekarzia in the prevention of disease progression to corneal ulceration was possible. Furthermore, the choice of the penalty score of 1 for rescue treatment and ulceration was considered arbitrary. Reassuringly, when modifying the weighting of the penalty, the outcome remained in favour of CsA with a statistically significant difference to vehicle for both low and high dose groups. Nevertheless, the results of the primary endpoint were difficult to interpret in terms of clinical relevance. In that sense, the CFS responder analyses, in particular those including Month 1 (although performed *post-hoc*) were considered more relevant.

Verkazia is recommended to be used 4 times a day including administrations at lunch and in the afternoon. Although treatment compliance was good throughout the study, this regimen may prove difficult in real-life, in particular for children going to the nursery or school. A less frequent instillation (morning and evening only) would be expected to be more convenient and increase compliance. Given the seasonal increase in signs and symptoms of the condition, whereby a reduction in disease severity is expected in most of the cases when the hot season is declining, a recommendation for QID dosing during VKC season, with the option to subsequently (at the end of the season) continue treatment at a reduced (BID) dose, once adequate control of signs and symptoms is achieved, was considered acceptable.

3.4. Unfavourable effects

The most common treatment-emergent adverse event (TEAEs) observed in the clinical development program were ocular and included eye pain (11%) and eye pruritus (9%) which were usually transitory and occurred during instillation. Up to 12 months, ocular TEAEs were considered to be treatment related in 22.2% (30/135) of patients treated with CsA 0.1% QID and 21.7% (30/138) in the CsA 0.1% BID group.

Only 5 serious adverse events were reported in patients receiving CsA eye drops and all events were judged unrelated to treatment. Only 3 patients receiving CsA discontinued due to a drug related AE compared to 5 patients in the vehicle arm.

Systemic TEAEs were reported in a similar proportion in the 3 treatment groups (14.6%, 15.1% and 15.3%, for the high dose group, low dose group and vehicle, respectively) including reports of upper respiratory tract infections. Given the immunosuppressive activity of CsA and since CsA is absorbed through the nasolacrimal duct after ocular instillation, although systemic exposure to CsA was overall negligible, a causal relation of these events to CsA could not be ruled out.

3.5. Uncertainties and limitations about unfavourable effects

The small number of VKC patients exposed to CsA eye drops (in total 189 patients) in the clinical development program, precluded realistic frequency estimations and the detection of rare events. In particular, only 84 and 49 patients received CsA at the strength and dose intended for commercial use (0.1% QID) for at least 4 and 12 months, respectively.

Given the immunosuppressive properties of CsA, there is a risk of related local adverse effects such as ocular infection or long latency events including corneal and conjunctival neoplasia and peri-ocular malignancy in particular when using CsA eye drops over prolonged periods of time. Toxicity related to accumulation of CsA in the ocular surface epithelium and peri-ocular tissues, and potentially deeper ocular structures also, is a theoretical consideration. Given that ciclosporin is known to be cytotoxic to some tissues, the possibility of penetration into deeper structures and toxicity to the lens epithelium should be considered. However, non-clinical studies showed neither accumulation nor significant penetration of deeper ocular tissues.

Overall, 3 cases of ocular infections were observed during the clinical trials program of Verkazia, none of which was considered related to treatment, and no cases of malignancies. In the absence of conclusive evidence of an increased risk, peri-ocular skin cancer, conjunctival or corneal neoplasia as well as development and exacerbation of ocular and peri-ocular infections were considered important potential risks. Linked to these concerns is the fact that only few patient data were available with an exposure to CsA 0.1% QID up to 12 months, whereas no data were available beyond 1 year of treatment. Long-term safety was therefore considered missing information in the RMP.

Use in patients with active or suspected ocular or peri-ocular infection is contraindicated and regular monitoring of the eye is advised when Verkazia is used for prolonged periods (more than 12 months). The product information furthermore informs that concomitant use of corticosteroid eye drops may potentiate the immunosuppressive effect. Together, these measures were considered sufficient to mitigate the potential risks related to a reduced local immune response. Finally, to further evaluate the potential risk of periocular skin cancer, conjunctival or corneal neoplasia in the paediatric population, a case control study linked to existing cancer registries is foreseen depending on the outcome of a feasibility study. Further long-term data are expected to be collected by means of routine Pharmacovigilance including periodic safety update reports and a follow-up questionnaire for reports of cases of periocular skin cancer, conjunctival or corneal neoplasia.

Use in pregnant and breast-feeding women was not studied. Given that studies in animals with systemic CsA have shown reproductive toxicity at high dosages and despite the low systemic exposure at therapeutic doses, Verkazia is not recommended in women of childbearing potential not using effective contraception and use during pregnancy and in lactating women is only recommended if the benefits outweigh the risks. Use in pregnant or lactating women is furthermore considered missing information in the RMP and will be monitored post-approval.

3.6. Effects Table

Table 22 Effects Table for Verkazia for the treatment of severe VKC in children from 4 years of age and adolescents

Effect	Short description	Unit	CsA 0.1% QID	CsA 0.1% BID	Vehicle	Uncertainties / Strength of evidence
Favourable Effects						
Reduction in corneal surface damage	CFS responder rate[(1)]	%	55.4	50.0	27.6	Odds ratios for CFS responders: • QID vs vehicle: 3.279 (p=0.005) • BID vs vehicle: 2.798 (p=0.010) Month 1 was only included in the responder analysis *post-hoc*, but results are in line with pre-defined analysis excl. Month 1.
	Penalty adjusted CFS score[(2)]	mean	2.06	1.93	1.34	
Improvement in symptoms	VAS symptom score[(3)]	mm	49.7	36.6	29.3	Difference: QID vs vehicle: -19.41 (p=<0.001) BID vs vehicle: -8.36 (p=0.103)
Unfavourable Effects[(4, 5)]						
Ocular TEAEs	Incidence of - all TEAEs - drug related TEAEs	%	 29.2 20.8	 24.7 17.2	 26.5 14.3	
Instillation site pain	Incidence of all TEAEs		9.4	7.5	4.1	
Instillation site pruritus			6.3	7.5	3.1	

Abbreviations: BID=twice daily; CSF= Corneal Fluorescence Staining; TEAE=treatment-emergent adverse event; QID=Four times daily; VAS=Visual Analogue Scale.

(1) Rate of responders at Month 1, 2, 3 and 4. Responders were defined as patients (1) with a CFS score equal or smaller than 50% of the baseline CFS, (2) who did not withdraw from the study for a reason possibly due to treatment, (3) free from occurrence of ulceration and (4) free from use of rescue medication.

(2) Composite efficacy score at 4 months, defined as the mean of the 4 efficacy scores taken at each monthly visit, based on the following equation: Patient's score at month X = CFS (Baseline) – CFS (Month X) + penalty(ies). A penalty of -1 was applied for use of rescue medication and in case of corneal ulceration

(3) Change in LS mean of the average of 4 symptom scores (photophobia, tearing, itching and mucous discharge) at Month 4 compared to baseline, assessed using a 100 mm VAS.

(4) Incidence rates as observed in the Double Masked Cohort.

(5) The limited size of the safety database precludes the detection of rare events and realistic frequency estimations.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A beneficial effect of Verkazia in the treatment of severe VKC has been demonstrated in terms of improvement in corneal health. A significantly larger proportion of patients met the CFS responder criteria during the first 4 months of treatment with CsA 0.1% than with vehicle [55.4%, 50.0% and

27.6% in the high dose group, low dose group and vehicle, respectively (p=0.005 and 0.010)]. Responders were defined as patients with an improvement of the CFS score by 50% or more from baseline without the need for rescue treatment or occurrence of ulceration, which was regarded clinically meaningful in the proposed target population. The observed increase in the response rates with both high and low CsA dose compared to vehicle (odds ratio of 3.279 and 2.798, respectively) represents a clinically relevant treatment benefit of Verkazia. This was further supported by consistent results for the primary composite efficacy endpoint, with a greater improvement of the penalty-adjusted CFS for CsA 0.1% compared to vehicle [difference in the LS mean vs. vehicle was 0.76 (p=0.007) and 0.67 (p=0.010)]. In addition, treatment with Verkazia helped alleviate symptoms with an improvement of the average symptom VAS score of -19.4mm (p<0.001) and -8.4mm (p=0.103) for the high dose and the low dose regimen, respectively, compared to vehicle. Given a minimum clinically significant difference of 10mm, these results supported a clinically relevant effect. Overall, consistent and clinically relevant results in favour of CsA 0.1% across the efficacy variables and subgroups were observed.

The safety assessment was limited by the small size of the safety database with only 49 patients being exposed to CsA 0.1% QID for 12 months and without any data beyond 1 year. The small samples size did not allow for accurate frequency estimations and rare adverse reactions may not have been detected. Despite this drawback, the available data showed that Verkazia was generally well tolerated. Adverse reactions were predominantly ocular and transient in nature occurring mainly during instillation of the eye drops. They included eye pain (11%) and eye pruritus (9%). Due to the immunosuppressive properties of CsA, uncertainties remained in relation to the risk of peri-ocular skin cancer, conjunctival or corneal neoplasia as well as the development and exacerbation of ocular and peri-ocular infections, in particular in patients using Verkazia over prolonged periods of time.

3.7.2. Balance of benefits and risks

Both the improvement in corneal surface defects and in symptoms observed with Verkazia in patients with severe VKC were considered clinically relevant. At the same time, treatment up to 12 months was well tolerated with mainly transient ocular adverse reactions including eye pain and itching in about 10% of patients. Overall, the CHMP was of the view that the benefits of Verkazia in the treatment of severe VKC in children from 4 years of age and adolescents outweighed its risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit-risk balance of Verkazia is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Verkazia is favourable in the following indication:

Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.

The CHMP 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).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

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

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0142/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.