EU Risk Management Plan

Active Substance: Ciclosporin

Date: 20 Sep 2025

EU Risk Management Plan – Version 7.5

IKERVIS (ciclosporin) 1mg/ml, eye drops, emulsion

VERKAZIA (ciclosporin) 1mg/ml, eye drops, emulsion

EU Risk Management Plan for:

- **IKERVIS® (ciclosporin) 1mg/ml, eye drops, emulsion**
- **VERKAZIA® (ciclosporin) 1mg/ml, eye drops, emulsion**

Foreword:

Medicinal products covered in this RMP are IKERVIS and VERKAZIA (ciclosporin) 1mg/mL eye drops emulsions. In this document, IKERVIS and VERKAZIA are also referred to an investigational product code NOVA22007.

In addition to IKERVIS and VERKAZIA, Santen Ltd (Japan) has ciclosporin-containing medicinal product registered as an orphan drug in Japan (trade name PAPILOCK Mini ophthalmic solution 0.1%). The product was developed under separate development program and it was approved on 11 October 2005 for the treatment of vernal keratoconjunctivitis (when insufficient efficacy is observed with other anti-allergic medications). The dosage of this product is one drop on affected eye(s) three times daily (no age-limitations mentioned in the product information). The relevant safety data related to PAPILOCK has been used in this RMP as supportive data especially for the characterization of risks for IKERVIS and VERKAZIA.

RMP version to be assessed as part of this application:

Version number	N°7.5
Data lock point for this RMP	02 Sep 2025
Date of final sign off	20 Sep 2025

Rationale(s) for submitting an updated RMP (7.5):

- The Post authorisation efficacy study (PAES) NVG14L127 was completed, reported and assessed. The RMP was updated to version 7.5 based on the conclusions.
- The summary of significant changes in RMP 7.5 is presented below.

Summary of significant changes in this RMP:

- Completion of IKERVIS PAES study added.
- Changes on Specific adverse event follow-up questionnaire according to the new version of the guideline on specific Adverse Reaction follow-up questionnaire

Other RMP versions under evaluation:

RMP version number	Submitted on	Submitted within
N/A		

Details of currently approved RMP:

IKERVIS:

Version number of last agreed RMP
Version number: N°7.2
Agreed within: IKERVIS® Centralised Marketing Authorisation Application

VERKAZIA:

Version number of last agreed RMP
Version number: N°7.4
Agreed within: VERKAZIA® Centralised Marketing Authorisation Renewal

QPPV/Contact details for this RMP:

QPPV name:	Tapio Kerttula
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ADR	Adverse Drug Reaction
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATU	Temporary use authorisation
BAK	Benzalkonium Chloride
BID	*Bis in die* (Twice a Day)
CHMP	Committee for Medicinal Products for Human Use
CFS	Corneal Fluorescein Staining
CKC	Cetalkonium Chloride
CSR	Clinical Study Report
CsA	Ciclosporin A
CTD	Common Technical Document
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
FAS	Full Analysis Set
FDA	US Food and Drug Administration
KCS	Keratoconjunctivitis Sicca
LDPE	Low-Density Polyethylene
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MA	Marketing authorisation
MAA	Marketing authorisation application
MGD	Meibomian Gland Disease
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PSUR	Periodic Safety Update Report
QD	*Quaque Die* (Once a Day)
QID	4 times per day
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SD	Standard Deviation
SDU	Signle dose unit (of eye drops)
SS	Sjögren's Syndrome
TEAE	Treatment Emergent Adverse Event
ULOQ	Upper limit of quantification
US	United States
VKC	Vernal Keratoconjunctivitis

Part I: Product(s) overview

Table Part I.1 – Product Overview: IKERVIS

Active substance(s) **(INN or common name)**	Ciclosporin (CsA)
Pharmacotherapeutic group(s) (ATC Code)	Other ophthalmologicals S01XA18
Marketing Authorisation Holder	SANTEN OY Niittyhaankatu 20 33720 Tampere FINLAND
Invented name in the European Economic Area (EEA)	IKERVIS® 1mg/ml, eye drops, emulsion
Authorisation procedure	Centralised procedure
Brief description of product including: • Chemical class • Summary of mode of action • Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	Chemical class: a cyclic polypeptide immunomodulator with immunosuppressant properties. Ciclosporin (also known as CsA) is a lipophilic cyclic polypeptide that has been used for several decades as a systemic immunosuppressant for the prevention of graft rejection following organ/tissue transplantation, and the treatment of various immune diseases, including ocular diseases. Ciclosporin has also been shown to possess anti-inflammatory properties. Studies in animals suggest that ciclosporin inhibits the development of cell-mediated reactions. Ciclosporin has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor (TCGF). It is also known to up-regulate the release of anti-inflammatory cytokines. Ciclosporin appears to block the resting lymphocytes in the G_0 or G_1 phase of the cell cycle. All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes and does not depress hematopoiesis or has any effect on the function of phagocytic cells. The resultant immunosuppressive and anti-inflammatory effects are non-toxic and reversible upon treatment cessation. In subjects with dry eye disease (DED), a condition that may be considered to have an inflammatory component, following ocular administration, ciclosporin enters corneal and conjunctival infiltrated T-cells and through its binding to cyclophilin A inactivates the phosphatase calcineurin. Ciclosporin-induced inactivation of calcineurin inhibits the de-phosphorylation of the transcription factor NF-AT and prevents its translocation into the nucleus, thus blocking the expression of anti-inflammatory cytokines such as IL-2 and the subsequent activation of the T-cell. The pharmacologic and clinical profile of IKERVIS suggests that it has the potential to provide consistent and efficacious anti-inflammatory effects, which translate into a clinical benefit for the ocular surface.

	IKERVIS is sterile, unpreserved, positively charged (i.e. cationic) oil-in-water (o/w), topical ophthalmic emulsion containing ciclosporin Ph. Eur. (CsA) 1 mg/ml (0.1% w/w). The emulsion comprises oil droplets stabilised by surfactants and dispersed in a continuous aqueous phase. A cationic surfactant is used to provide a positive charge to the oily droplets and to stabilise the emulsion system by achieving an electrostatic repulsion between the oil droplets. The emulsion formulation is specifically designed to prolong the residence time of each eye drop on the epithelial layer of the eye: the positively charged oil droplets adhere to the negatively charged surface moieties by electrostatic attraction (Rabinovich-Guilatt 2004). The cationic charge is brought by cetalkonium chloride (CKC), known to play an important role both in the emulsion stability and biological performances of the product (ocular absorption of CsA).
Hyperlink to the Product Information	*Include a link or reference to the proposed PI in the eCTD sequence.* *If no updated PI is submitted with the procedure, the link should direct to the latest approved PI.*
Indication(s)	**Approved indication**: Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.
Dosage and route of administration in the EEA	Ocular use. The recommended dose is one drop in the conjunctival sac of the affected eye(s) once daily at bedtime. For single use only
Pharmaceutical form(s) and strength(s)	Eye drops, emulsion 1ml of emulsion contains 1 mg of ciclosporin IKERVIS 1mg/ml is supplied in single-dose, low–density polyethylene (LDPE) container, filled with 0.3 ml fill volume.
Is/will the product be subject to additional monitoring in the EU?	No
Country and date of first authorization worldwide	EU, Norway, Liechtenstein and Iceland 19 March 2015
Country and date of first launch worldwide	France 08 June 2015
Country and date of first authorization in the EEA	EU, Norway, Liechtenstein and Iceland 19 March 2015

Table Part I.2 – Product Overview: VERKAZIA

Active substance(s) **(INN or common name)**	Ciclosporin (CsA)
Pharmacotherapeutic group(s) (ATC Code)	Other ophthalmologicals S01XA18
Marketing Authorisation Holder	SANTEN OY Niittyhaankatu 20 33720 Tampere FINLAND
Invented name in the European Economic Area (EEA)	VERKAZIA 1mg/ml, eye drops, emulsion
Authorisation procedure	Centralised procedure (Orphan medicinal product; EU/3/06/360)
Brief description of product including: • Chemical class • Summary of mode of action • Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	Chemical class: a cyclic polypeptide immunomodulator with immunosuppressant properties. Ciclosporin (also known as CsA) is a lipophilic cyclic polypeptide that has been used for several decades as a systemic immunosuppressant for the prevention of graft rejection following organ/tissue transplantation, and the treatment of various immune diseases, including ocular diseases. Ciclosporin has also been shown to have an anti-inflammatory effect. Studies in animals suggest that ciclosporin inhibits the development of cell-mediated reactions. Ciclosporin has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor (TCGF). It is also known to up-regulate the release of anti-inflammatory cytokines. Ciclosporin appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle. All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes and does not depress haematopoiesis or has any effect on the function of phagocytic cells. In patients with VKC, ciclosporin, following ocular administration, is passively absorbed into T-lymphocyte infiltrates in the cornea and conjunctiva and inactivates calcineurin phosphatase. Ciclosporin-induced inactivation of calcineurin inhibits the dephosphorylation of the transcription factor NF-AT and prevents NF-AT translocation into the nucleus, thus blocking the release of pro-inflammatory cytokines such as IL-2, thus blocking T-lymphocytes activation. Blocking NF-AT further interferes in the allergic process. Ciclosporin also inhibits 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.

	VERKAZIA is sterile, unpreserved, positively charged (i.e. cationic) oil-in-water (o/w), topical ophthalmic emulsion containing ciclosporin Ph. Eur. (CsA) 1 mg/ml (0.1% w/w). The emulsion comprises oil droplets stabilised by surfactants and dispersed in a continuous aqueous phase. A cationic surfactant is used to provide a positive charge to the oily droplets and to stabilise the emulsion system by achieving an electrostatic repulsion between the oil droplets. The emulsion formulation is specifically designed to prolong the residence time of each eye drop on the epithelial layer of the eye: the positively charged oil droplets adhere to the negatively charged surface moieties by electrostatic attraction (Rabinovich-Guilatt 2004). The cationic charge is brought by cetalkonium chloride (CKC), known to play an important role both in the emulsion stability and biological performances of the product (ocular absorption of CsA).
Hyperlink to the Product Information	*Include a link or reference to the proposed PI in the eCTD sequence.* *If no updated PI is submitted with the procedure, the link should direct to the latest approved PI.*
Indication(s)	**Approved indication**: Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.
Posology and route of administration in the EEA	Ocular use. The recommended dose is one drop of VERKAZIA 4 times a day (morning, noon, afternoon and evening) to be applied to each affected eye during the VKC season. If signs and symptoms of VKC persist after the end of the season, treatment can be continued at the recommended dose or decreased to one drop twice daily.
Pharmaceutical form(s) and strength(s)	Eye drops, emulsion 1ml of emulsion contains 1 mg of ciclosporin VERKAZIA 1mg/ml is supplied in single-dose, low–density polyethylene (LDPE) container, filled with 0.3 ml fill volume.
Is/will the product be subject to additional monitoring in the EU?	No
Country and date of first authorization worldwide	EU, Norway, Liechtenstein and Iceland 06 July 2018
Country and date of first launch worldwide	N/A

Country and date of first authorization in the EEA	EU, Norway, Liechtenstein and Iceland 06 July 2018

Part II: Module SI - Epidemiology of the indication(s) and target population

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	31 October 2016
Version number of this RMP Module	3

Part II: Module SI - Epidemiology of the indication and target population

SI.1 Epidemiology of the disease

IKERVIS

Indication: Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Brand Name of concerned product: IKERVIS® 1mg/ml, eye drops, emulsion

Dry eye disease (DED) is one of the most common ophthalmic diseases. Based on the 2007 Dry Eye Workshop (DEWS) report, the prevalence of dry eye ranges from 5%-15% in the USA, Australia, and Europe to 30-50% in Asia. The highest prevalence is observed in Asian subjects and in subjects of Hispanic origin. DED is more common in women and the prevalence increases with age.

Historically, DED was classified as due to either insufficient production or impaired stability of tears. At the 2007 International DEWS (DEWS 2007), the term 'dry eye disease' (DED) was accepted and defined as 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface'. This definition was selected as reflecting the current understanding of the disease. Regardless of which of the initiating factors or groups of factors result in the presentation of dry eye, there is a common final pathway for expression of the disease. There is now evidence (Labetoulle 2013) that the previous dichotomous classification distinguishing between insufficient production and impaired stability of tear film does not fit with the reality of clinical practice, since any abnormality of the ocular surface can trigger disequilibrium in all the other components of tear dynamics. This results in a vicious circle (Baudouin 2007) with as many ways to enter as there are causes of destabilization of the ocular surface. Eventually, the patient develops a self-sustaining, and finally severe, DED.

DED is a chronic problem and its economic burden has significantly increased in recent years (Bielory 2013). DED also affects the quality of life: the impact of fairly severe DED has been reported to compare with dialysis and severe angina (Schiffman 2003). The pathogenesis of DED is not fully understood; however, it is recognized that inflammation has a prominent role in the development and amplification of the signs and symptoms of DED (Stevenson 2012). DED prognosis shows considerable variance, depending upon the severity of the condition and the severity of the underlying pathology. By definition, dry eye can cause damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort (Lemp 2008). Once DED has developed, inflammation becomes the key mechanism of ocular surface injury. There are very few approved pharmacological treatments for DED in the world, and subjects report using artificial tears on a frequent basis (Kymionis 2008). Most patients have mild-to-moderate complaints and can be treated symptomatically with lubricants for long periods of time. However, patients with more severe conditions such as Sjögren syndrome or those with severe keratitis that can cause major ocular complications, such as infections or ulcers with irreversible loss of visual acuity, represent a group of patients with a worse prognosis (Asbell 2010) and in need of more effective treatments. These patients with severe DED are trapped in a vicious cycle of inflammation and ocular surface injury. They complain of persistent and recurrent symptoms related to their DED. These symptoms usually correlate poorly with the objective clinical findings such as corneal erosion, punctate keratopathy, epithelial defects, corneal ulceration (sterile or infected), corneal neovascularisation, corneal scarring, or even corneal perforation (Stonecipher 2005, Baudouin 2007, Johnson 2009, Labetoulle 2012).

There has been a noticeable increase in knowledge regarding the pathophysiology of DED in the last two decades. It is now recognised that the ocular surface and tear-secreting glands function as an integrated unit to maintain the tear supply and to clear used tears. Dysfunction of this functional unit results in an unstable and poorly maintained tear film causing ocular signs and symptoms. It is currently recognised that Meibomian gland dysfunction may well be the leading cause (Nichols 2011). Dysfunction may develop from aging, a decrease in supportive factors (such as hormones), systemic inflammatory diseases (such as rheumatoid arthritis or Sjögren syndrome) or ocular inflammatory disorders and local immune/autoimmune mechanisms (ocular surface antigens, autoantibodies TH1/TH17), ocular surface diseases (such as viral keratitis) or surgeries that disrupt the trigeminal afferent sensory nerves (e.g.

LASIK), or medication (e.g. antihistamines, anticholinergics or antidepressants) that disrupt the efferent cholinergic nerves that stimulate tear secretion. This has led to a paradigm shift from simply lubricating and hydrating the ocular surface with artificial tears to strategies that stimulate natural production of tear constituents, maintain ocular surface epithelial health and barrier function, and inhibit the inflammatory factors that adversely impact the ability of ocular surface and glandular epithelia to produce tears. The use of ophthalmic CsA undoubtedly falls into that approach.

The main existing treatment options:

Very few products are registered for DED in Europe and many are available over-the-counter. Pharmacy compounded CsA formulations in olive or castor oil with strength from 0.03% to 2% have been widely used for decades to treat signs and symptoms of ocular diseases such as DED or VKC (Alcimed 2014). There dosage regimen of the pharmacy compounded products vary from 1 to 4 drops daily, even up to up to 12 instillations per day.

IKERVIS is the first registered topical ciclosporin for severe keratitis in DED patients in Europe. IKERVIS represents a significant advance in anti-inflammatory therapy for patients with DED, consistent with both clinical practice (Alcimed 2014) and clinical recommendations (DEWS 2007). IKERVIS can replace hospital pharmacy compounded ciclosporin formulations, which are widely used but poorly controlled.

The important alternatives medications used to treat DED include:

Topical corticosteroids: these can be used only for short periods in order to decrease ocular surface inflammation inhibiting MMPs (matrix metalloproteinasis), inflammatory cytokines and adhesion molecule production (Kymionis 2008). However they should not be administered for long-term use owing to their adverse effects such as onset of glaucoma or cataract. They also promote bacterial infection.

Tear substitutes (including those registered as medical devices): these are used extensively by patients to treat the symptoms of DED (Yagci 2014), but are not very effective on severe corneal lesions since they do not treat the underlying inflammation.

Topical antibiotics: amongst antibiotics, tetracyclines have anti-inflammatory properties such as inhibition of MMPs and interleukine-I (IL-I) production, and oral treatments decrease ocular surface symptoms in patients with ocular rosacea (Kymionis 2008). Otherwise, topical azithromycin or systemic antibiotics (second generation cyclins, azithromycin) are prescribed for cases of blepharitis and Meibomian Gland Dysfunction.

Poly-unsaturated fatty acids (omega-3 and omega-6): used as adjuvant treatment these may improve the quality of lipid secretions and be beneficial in the disease-modifying treatment of dry eye disease. However, there is no firm proof of their clinical efficacy (Lemp 2008).

Secretagogues: used to increase the secretion of saliva and tears, they are more effective in the mouth than the eye, and their secondary effects limit their use.

Tear duct plugs (punctal plugs): these are interesting therapeutic options but their efficacy varies. Tear duct plugs may help to reduce severe keratitis (such as filamentary keratitis) by preventing tear secretion. However, the presence of inflammatory mediators in the tear film explains the frequent treatment failures. Indeed, blocking the tear ducts may exacerbate inflammation by prolonging the contact time of immune factors in the tears. This treatment is only recommended once any ocular inflammation has been controlled by an anti-inflammatory treatment (Lemp 2008). In clinical practice, this is often after long-term anti-inflammatory treatment with a topical ciclosporin (Labetoulle 2013).

Autologous serum eye drops: this treatment is of particular interest as an adjuvant to classical therapies for severe forms of dry eye disease, especially neurotrophic keratitis, persistent corneal ulcers or corneal healing disorders. The preparation of autologous serum is a complex process, carried out only in a few hospitals. The eye drops must be stored at -80°C and have a very limited shelf-life after thawing, rendering this treatment highly impractical.

Moisture chamber glasses: moisture chamber glasses, which may be tinted, help protect the eyes from environmental aggression and increase the humidity around the eyes.

Eyelid warming devices are also indicated for blepharitis and to relieve the symptoms of Meibomian Gland Dysfunction (MGD) by facilitating eyelid hygiene. Both medical devices relieve symptoms and improve the tear film.

Scleral lenses: for refractory cases of dry eye disease, scleral lenses may be of great help (Lemp 2008). These large lenses have been around for a long time but modifications made of new materials permeable to oxygen are being introduced. However, because they are not manufactured on a large scale, they are not easily available. Moreover, they are not easy to manipulate and this may lead to treatment failure.

Surgery to save the cornea:

- *Amniotic membrane grafting* can be performed to improve the healing of corneal ulcers that might otherwise perforate.

- *Temporary tarsorrhaphy* may be performed in the event of malocclusion

Important co-morbidities:

DED, either alone or in combination with an underlying inflammatory and systemic condition e.g. Sjögren syndrome, is a frequent cause of ocular irritation that leads patients to seek ophthalmologic care. While the symptoms often improve with treatment, the disease is usually not curable, which may be a source of patient and physician frustration. The American Academy of Ophthalmology's guidelines for diagnosis, treatment, and management of DED (AAO 2011) postulates that, alone or in combination with other conditions, dry eye can be a cause of visual morbidity and may compromise results of corneal, cataract or refractive surgery. Patients with DED often have many contributing factors (e.g. female sex, older age, postmenopausal estrogen therapy, a diet that is low in omega 3, refractive surgery, vitamin A deficiency, radiation therapy and bone marrow transplantation). Other risk factors may include diabetes mellitus, HIV and human T cell lymphotropic virus infection, connective tissue diseases, systemic cancer chemotherapy, and medication iatrogenic side effects, such as with isotretinoin, antidepressants, anxiolytics, beta-blockers, or diuretics (DEWS 2007). It is imperative to treat any causative factors that are amenable to treatment. Tear replacement, though widely used by patients, is frequently unsuccessful when used as the sole treatment if additional causative factors are not concomitantly addressed.

The patient population involved in IKERVIS studies and more specifically in the 2 Phase III (SANSIKA and SICCANOVE) studies reflect well the general population affected by DED. Patients were predominantly older female with a chronic and persistent severe DED lasting for 8-9 years in average, and for whom artificial tears was the usual background treatment. More than a third of them reported Sjögren syndrome.

VERKAZIA

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

Brand Name of concerned product: VERKAZIA 1mg/ml, eye drops, emulsion

Vernal keratoconjunctivitis (VKC) is a severe allergic disease, characterised by chronic ocular surface inflammation with seasonal relapses. It is a potentially sight-threatening disease with a high risk of visual impairment (Leonardi 2013). Visual loss may be due to corneal complications such as ulcers, scarring, corneal opacities, limbal stem cell deficiency, astigmatism and keratoconus. The disease mainly occurs in children with a common age of onset between 4 and 7 years of age, and a male preponderance. Symptoms occur before the age of 10 in 80% of cases and boys are affected 2-4 times more frequently than girls (Leonardi 2002, Pucci 2002, Bonini 2004). While it is considered a long-term disease with an average duration of 4–8 years, VKC generally resolves before or just after puberty (Bielory 2000, Leonardi 2013).

On 6 April 2006, when NOVA22007 was designated as an orphan medicinal product in the European Union

for the treatment of VKC (EU/3/06/360), VKC was said to affect 1 to 3 in 10 000 people in the EU. For the purpose of the designation, the number of patients affected by the condition was estimated based on four studies conducted in the UK, Sweden, France and Italy. This led to an estimated number of patients with VKC between 46,000 and 138,000 (i.e. 1 to 3 in 10,000 persons) at mid-2005 in the EU 25-countries including Iceland, Liechtenstein and Norway, which is below the threshold for orphan designation (5 in 10,000). VKC has been reported from almost all continents. The disease was mostly described around the Mediterranean with most cases reported from Italy (Leonardi 2006). VKC is indeed more prevalent in warm climates, particularly the Middle-East-Mediterranean region and North Africa, but also West Africa, Central America and some regions in India while being rare in most of North America and Western Europe. However, Japan with a milder climate than most countries in Asia also reported a large number of VKC. This indicates that warm weather conditions may not be absolutely necessary for the development of the disease. A recent epidemiologic survey of 3003 ophthalmologists from 6 EU countries (Finland, France, Italy, the Netherlands, Norway, and Sweden) concluded that VKC prevalence was estimated at 3.2/10,000 with a prevalence of VKC with corneal complications of 0.8/10,000 (Bremond-Gignac 2008).

VKC can be divided into three distinct phenotypes: tarsal, limbal, and mixed VKC (De Smedt 2013). Limbal VKC identified by a broad thickened, circumferential gelatinous opacity of the limbus and by Horner-Trantas dots has been reported more often from West India and Africa. Palpebral VKC marked by cobblestone papillae on the superior tarsal conjunctiva, is more frequent in Europe and North America. Large papillae of different shape and size, usually greater than 1 mm in diameter, on the upper tarsal conjunctiva characterize the tarsal form, while Trantas' dots and infiltrates on the limbus are typical of the limbal form. It is unclear why this difference exists, despite the fact that these two clinical presentations can coexist. The rate of allergic sensitization was reported to be higher in tarsal VKC than in those with the limbal form, indicating that the pathogenesis of the two types of disease could be different. As disease severity in patients with limbal VKC is noted to be milder than in those with tarsal and mixed VKC, there is some speculation that limbal VKC may be the early stage of VKC, although studies indicating the progress from one type of VKC to the other are still lacking (Vichyanond 2014). A seasonal pattern is encountered in temperate countries, suggesting that atmospheric conditions promote flare-ups during spring and summer. The perennial form occurs more frequently in hot countries. Although VKC generally subsides with or after puberty, evolution towards atopic keratoconjunctivitis can be observed at an adult age. VKC is a long- lasting disease, since most studies confirm an average duration of 4-8 years (Bremond-Gignac 2008).

VKC is differentiated from other ocular allergic conditions, such as seasonal or perennial allergic conjunctivitis, infectious conjunctivitis or ocular rosacea in children, through a comprehensive clinical history and ophthalmic examination.

The main existing treatment options:

Currently available topical drugs for severe VKC belong to several pharmacologic classes: vasoconstrictors, antihistamines, mast cell stabilisers, 'dual-acting' agents (with antihistaminic and mast cell stabilising properties), non-steroidal anti-inflammatory agents, corticosteroids and immunosuppressive drugs (Table 1). 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 year(s). None of them have been approved for the treatment of VKC or more specifically for severe VKC. All these drugs are merely palliative and do not eliminate the complex immune process that initiates and perpetuates the allergic ocular surface inflammation, which explains disease recurrences when the therapy is discontinued (Leonardi 2013).

The Figure 1 illustrates the treatment of different VKC grades. Topical steroids, anti-allergens and lubricant eye drops/vasoconstrictor eye drops are concomitantly used with ciclosporin. Table 1 lists the common medications, their indication and limitations.

Table 1: Commonly used therapies for VKC in Europe (Leonardi 2013)

Class	Drug	Indication	Comments
Vasoconstrictor/ antihistamine	Naphazoline/pheniramine	Rapid onset of action	Short duration of action Tachyphylaxis

Class	Drug	Indication	Comments
combinations		Episodic itching and redness	Mydriasis Ocular irritation Hypersensitivity Hypertension Potential for inappropriate patient use
Antihistamines	Levocabastine Emedastine	Relief of itching Relief of signs and symptoms	Short duration of action Frequently does not provide complete disease control when used alone
Mast cell stabilizers	Sodium cromoglicate Nedocromil Lodoxamide NAAGA Pemirolast	Relief of signs and symptoms	Long-term usage Slow onset of action Prophylactic dosing Frequently does not provide complete disease control when used alone
Antihistamine/mast cell stabilizers (dual-acting)	Alcaftadine Azelastine Bepotastine Epinastine Ketotifen Olopatadine	Relief of itching Relief of signs and symptoms	Bitter taste (azelastine) No reported serious side effects Frequently does not provide complete disease control when used alone
Corticosteroids	Loteprednol Fluormetholone Desonide Rimexolone Dexamethasone Betamethasone	Treatment of allergic inflammation Use in moderate to severe forms	Risk for long-term side effects No mast cell stabilization Potential for inappropriate patient use Requires close monitoring

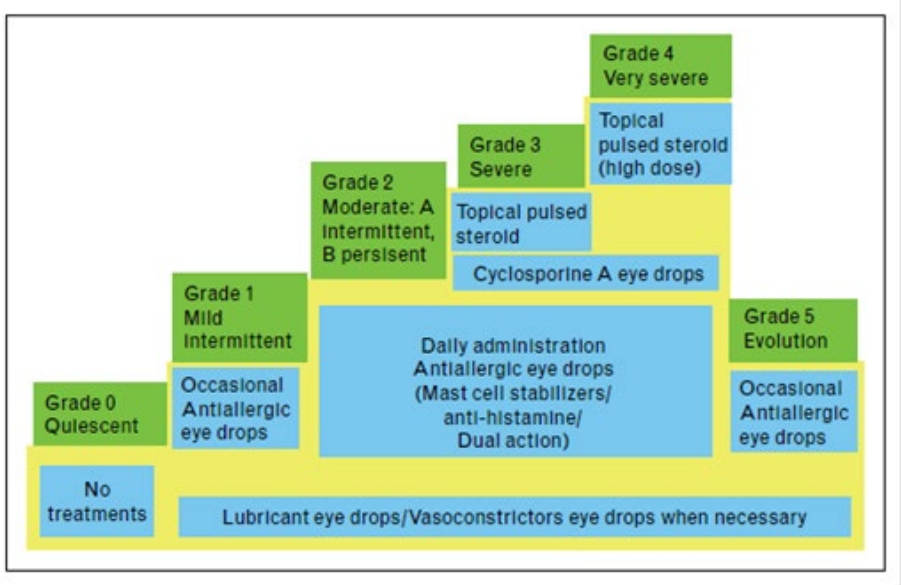

Figure 1 : Different therapeutic approach proposed for the different VKC grades (Sacchetti 2010).

A systematic review and meta-analysis of the efficacy of topical treatments for VKC including antihistamines, mast cell stabilisers, NSAIDs, corticosteroids and immunodulators evaluated in

randomised clinical trials was published in 2007. Of the 27 studies meeting the standards of methodological quality using the Delphi list only 2 investigated the use of corticosteroids in patients with VKC, neither of which evaluated dexamethasone, the only corticosteroid registered in the EU for the treatment of VKC. It was the conclusion of the authors that despite the availability of a variety of commonly used therapies for VKC there is a lack of evidence to support the recommendation of one specific type of medication to treat VKC. The authors also identified the need for standard criteria to assess diagnosis and therapy and for long-term data to inform disease control and complications (Mantelli 2007). In a more recent review the author emphasized the beneficial effect of topical CsA for the long-term treatment of VKC, by significantly improving signs and symptoms without significant side effects (Leonardi 2013).

Non-pharmacological eye drops: symptoms of eye irritation, burning sensation, and blurring of vision are caused by the presence of inflammatory cytokines and cellular infiltrates on the conjunctival surfaces. Rinsing of the eye with adequate amounts of cool normal saline removes these cellular debris and toxic substances and can bring some symptoms relief. However, rinsing should be repeated several times a day during the acute exacerbations. Application of preservative-free artificial tears can also be used to aid in stabilization of the tear film, act as eyewash, and dilute the concentration of the allergens and mediators in tears. Despite the frequent use of eye rinsing during exacerbations and in maintenance therapy, their efficacy has not been evaluated systematically and is merely symptomatic.

Ocular antihistamines: the use of topical antihistamines alone has not produced satisfactory results either, despite the fact that histamine is the major mediator in this disease. For instance, topical levocabastine was found to be inferior to lodoxamide in alleviating ocular symptoms/signs such as itching, tearing, and photophobia (Verin 2001). Because of their promising roles in allergic eye inflammation, newer antihistamines with extended properties such as levocabastine hydrochloride 0.5mg/ml, emedastine difumarate 0.5mg/ml or olopatadine 1mg/ml have been increasingly used for VKC despite the unavailability of clinical data.

Topical mast cell stabilisers and dual-acting agents: used as first-line drugs for VKC, they are generally safe with minimal ocular side effects, although transient burning or stinging may occur upon application. The recommended dosing schedule is 4–6 times daily, with a loading period of at least 7 days and an onset of activity after as much as 2 weeks. Among these agents, cromolyn sodium and lodoxamide have been extensively evaluated. Interest in applying cromolyn (Disodium cromoglycate DSCG) eye solution for VKC treatment started as early as the late 1970s. Both 2% and 4% DSCG solution were found to be superior to placebo in reducing signs and symptoms of VKC. However, symptoms in severe VKC often persisted even after a prolonged use, and persistence of symptoms could be observed in up to 42% of eyes treated with DSCG (Leonardi 1997). Lodoxamide, a mast cell stabilising agent with inhibitory effects on neutrophil and eosinophil migration, which has been demonstrated to be more effective than DSCG for the treatment of VKC patients became a standard therapy for VKC during the early 2000s (Leonardi 1996). N-acetyl aspartyl glutamic acid (NAAGA) 6% known to inhibit leukotriene synthesis, histamine release by mast cells, and complement-derived anaphylatoxin production, has also been used in Europe as topical eye drops in the treatment for VKC (Leonardi 2007). Other immunomodulators that have been tried at with varying degree of efficacy in a limited number of studies include mitomycin-C, mipragoside, and ketorolac.

Topical Corticosteroids: As exacerbations are common in VKC despite a continuing use of mast cell stabilisers as maintenance therapy, patients often need topical corticosteroids pulse therapy for disease control (De Smedt 2013). Similarly, persistent severe symptoms, thick mucous discharge with moderate to severe corneal involvement, numerous and inflamed limbal infiltrates and/or giant papillae, indicate a need for corticosteroids. However, corticosteroids should be avoided as first line treatment of VKC. If steroids are used, those with low intraocular absorption, such as hydrocortisone, clobetasone, desonide, fluorometholone, loteprednol, difluprednate and rimexolone, should be used first. Dosages are chosen based on the inflammatory state of the eye, with therapy prescribed in pulses of 3–5 days. Loteprednol etabonate is usually indicated for 7–8 days in the treatment of the acute phase. Prednisolone, dexamethasone, or betamethasone should be used only when the above-mentioned first-choice steroids have proven ineffective. Steroid–antibiotic combination eye drops should be avoided, as VKC is an allergic inflammation, rather than an infection.

Although significant symptomatic and clinical improvements have been reported, long term use of corticosteroids should be avoided due to well-known ocular adverse effects, including increases in intraocular pressure (IOP), induction or exacerbation of glaucoma, formation of cataracts, delayed wound healing, and increased susceptibility to infection. These adverse effects depend, in part, on the structure, dose, duration of treatment and gender (McGhee 2002). It has been shown that increased IOP can develop within 2 weeks of the use of topical steroids (Kersey 2006). Forty-one of 145 (28.3%) patients with severe VKC in a Singapore case series developed a corticosteroid response, of which eight (5.5%) progressed to glaucoma (Ang 2012).

Calcineurin Inhibitors & other immunomodulators: Ciclosporin A (CsA), 0.5% to 2% ophthalmic emulsion in olive or castor oil has been used for decades as an alternative to steroids in moderate to severe forms of VKC. CsA has thus been used via hospital-compounded preparations. So far, unavailability of a commercial preparation of topical CsA, technical difficulties in dispensing eye drops and legal restrictions of CsA use in several EU countries, preclude a widespread use for children suffering from VKC (Leonardi 2013). No significant side effects, except for a burning sensation during administration, have been reported (Utine 2010).

Tacrolimus hydrate, another immunomodulator, similarly to CsA, was granted orphan drug status for the treatment of VKC in 2004[1] as it was expected to bring potential significant benefit for the treatment of VKC. However, the product was subsequently withdrawn from the Community Register in 2010 on the request of the sponsor. A prospective double-masked randomized comparative trial comparing the efficacy of 0.1% tacrolimus ophthalmic ointment with CsA 2% showed that both were equally effective in the treatment of VKC (Labcharoenwongs 2012).

Topical mitomycin-C 0.01% used short-term and at low-dose, has been considered for treating acute exacerbations in patients with severe VKC refractory to conventional treatment. A significant decrease in signs and symptoms compared with placebo was shown at the end of the 2-week treatment period. Unavailability of commercial topical preparations, the short duration of studies, and the lack of data on the safety profile and long-term outcomes are major limitations in recommending mitomycin for the treatment of VKC.

Surgical treatment: rarely, VKC patients require a surgical approach. Surgical removal of corneal plaque is recommended only in persistent cases to alleviate severe symptoms and to allow corneal re-epithelization. Giant papillae excision with intra-operative 0.02% mitomycin-C followed by CsA topical treatment may be indicated only in cases of mechanical pseudoptosis, coarse giant papillae and continuous active disease. Other invasive procedures such as oral mucosa grafting should otherwise be avoided as treating only the complications and not the underlying disease, and mainly inducing unnecessary scarring.

Important co-morbidities:

Family atopy is very common in VKC patients, as well as personal atopy. 40-75% of VKC subjects have asthma, hay fever or eczema (Bonini 2000). In addition to itching and grittiness usually observed in common ocular allergy, other highly specific symptoms are photophobia and tearing, which are particularly disabling. Palpebral thickening may result in pseudo-ptosis. The mucus discharge is thick and abundant and adheres to the giant cobblestones of the upper tarsus. Trantas' dots and large cobblestone papillae are indicative of the condition.

VKC sufferers have a characteristic ropey, stringy mucous and/or serous discharge, and corneal complications, such as superficial punctate keratopathy, and shield ulcers are common. Moderate to intense conjunctival hyperaemia, intense itching, photophobia, mild to moderate chemosis, foreign-body

1 http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005704.pdf

sensation, and pain are typical signs and symptoms which may be very intense upon awakening, causing frequently what is called the 'morning misery'.

VKC can cause severe visual complications (Leonardi 2013). Ocular surface remodelling leads to severe suffering and complications, such as corneal ulcers and scars. Despite the absence of mast cells and lymphocytes, with only few immature resident dendritic cells, the cornea can be involved in VKC inflammation, taking the form of a superficial punctate keratitis or epithelial macroerosions, or shield ulcers. Keratitis that occurs in up to 50% of cases (Bremond-Gignac 2002) and shield ulcers are sight-threatening complications (Tabbara 1999). Children with VKC have a high incidence of keratoconus and more abnormal corneal topography patterns compared with normal eyes. Other complications include side effects from chronic topical steroids use, such as increased intraocular pressure, glaucoma, cataract and infections, and around 6% of patients develop a visual impairment (Bonini 2003).

The prolonged and recurrent nature of the disease affects daily life activities, physical activity, social interactions and somatic sensation of the young patients (Sacchetti 2007). Moreover, the severe signs and symptoms of the disease result in frequent ophthalmologic controls, influencing children school activities and working days for their parents with a noticeable economic cost impact for National Health Systems.

Part II: Module SII - Non-clinical part of the safety specification

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/MAA name	SANTEN OY

Data lock point for this module	31 October 2016
Version number of this RMP Module	3

Part II: Module SII - Non-clinical part of the safety specification

IKERVIS/VERKAZIA

Key safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity/carcinogenicity	The data on animals and humans presented in the literature and in standard medical reference texts such as Martindale (Sweetman 2009) have indicated that CsA is unlikely to be genotoxic (Olshan 1994). CsA is clearly referred in the literature as a non-genotoxic human carcinogen (McClain 2001, Hernandez 2009). Various immonosuppressive drugs have been associated with an increased incidence of lymphoproliferative disorders and other malignancies, particularly of the skin. These lymphoproliferative lesions may regress after dose reduction or treatment cessation (Starzl 1984). Thus, only excessive immunosuppression may allow for uncontrolled cellular growth, something that is not expected at the doses used with an ocular topical application of IKERVIS 1 mg/ml or VERKAZIA, even in eye tissues. In addition, no cases of malignancy were associated with topical formulation of CsA (Bohringer 2008). As a consequence, no experiments assessing the potential genotoxicity or carcinogenicity of IKERVIS or VERKAZIA were undertaken.
Reproductive toxicity	CsA toxicology profile was evaluated in different animal species, and was shown to have no myelotoxic, teratogenic, mutagenic or carcinogenic effects (Ryffel 1983). There are no studies with IKERVIS or VERKAZIA in breast-feeding women. CsA is known to be excreted in human milk following oral administration. Since the level of systemic absorption of CsA following IKERVIS or VERKAZIA application is negligible, it is unlikely that CsA would reach the breast milk and be passed to the infant while breastfeeding.
Quaternary ammonium toxicity (CKC/BAK)	IKERVIS /VERKAZIA is an unpreserved cationic oil-in-water emulsion which positive charge is brought by the cationic surfactant cetalkonium chloride (CKC). Kurup et al (Kurup 1992) have demonstrated that only the free form of the quaternary ammoniums (BAK and/or CKC) present in the aqueous phase is available for antibacterial activity and thus exert preservative properties, as well as deleterious action on ocular surface cell membranes. This was confirmed by (Liang 2008) with a 0.02% w/w BAK-containing cationic emulsion being much better tolerated than a 0.02% w/w BAK solution by the sensitive ocular surface cells. This study also confirmed that the CKC-containing emulsion is better tolerated than the BAK-containing emulsion. Good laboratory practice 28-day local ocular tolerance studies performed in rabbits, have also demonstrated that repeated instillations (up to 6 times daily) of CKC-containing IKERVIS 1mg/ml/VERKAZIA 1mg/ml emulsion are safe and well tolerated.
Phototoxicity and photoallergy	Considering the absence of phototoxic or photoallergic potential demonstrated in non-clinical studies, the risk to humans is very low.

Conclusions on non-clinical data

During the development of Santen CsA product, the non-clinical studies did not show any new safety concern. There is no need to submit additional non-clinical data for IKERVIS. This was judged acceptable by the CHMP in a CHMP/SAWP completed in December 2010.

Considering that the external parts of the eye are fully developed in the target population, that the intraocular and systemic exposure to CsA following ocular instillations is very low, and considering the long history of use of CsA hospital preparations in VKC children population, no studies in juvenile animals were considered necessary. Also, no additional non-clinical data has been seen needed for VERKAZIA because the product formulation is the same as for IKERVIS.

Part II: Module SIII - Clinical trial exposure

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	31 October 2016
Version number of this RMP Module	2

Part II: Module SIII Clinical trial exposure

SIII.1 Brief overview of development

IKERVIS

The clinical development of IKERVIS consisted of 4 clinical studies. Later on, one additional clinical study has been conducted:

➢ ***One pivotal Phase III randomised double masked vehicle controlled clinical study****:*

Study NVG10E117, the so called SANSIKA Study, was a multi-centre, randomised, double-masked, 2 parallel arms, vehicle controlled, 6-Month study, with a 6 month open label treatment safety follow-up period. This study was designed to evaluate the efficacy and safety of IKERVIS 1 mg/ml eye drops, administered once daily ***to treat Dry Eye Disease (DED) in adult patients with severe keratitis that was not improving despite treatment with tear substitutes.***

The primary objective of the study was to demonstrate the superiority of IKERVIS administered once daily versus vehicle after a 6-Month treatment period. The secondary objective was to evaluate the ocular tolerability and overall ocular safety of IKERVIS administered once daily over 12 months at two time points: at Month 6, after the randomised, double-masked study treatment period (Part 1) and at Month 12, after open label safety treatment follow-up period (Part 2).

➢ ***Three supportive randomised double masked, multicentre vehicle controlled clinical studies:***

Study N09F0502 was a Phase IIa, multicentre, double-masked, randomised, parallel group study designed to evaluate IKERVIS ***in Sjögren patients with moderate to severe DED***. The main objective was to assess the ocular tolerance, ocular safety and systemic safety of 3 different concentrations of IKERVIS (CsA 0.025%, 0.05%, 0.1%) and its vehicle after 3 months of treatment (all patients receiving in a double masked fashion, one drop twice daily).

Study (ORA) NVG08B112 was a double-masked vehicle controlled randomised Phase IIb study performed ***in mild to moderate DED patients*** using IKERVIS 0.05% and 0.1% and vehicle given once a day for 3 months. The study was conducted in a Controlled Adverse Environment (CAE). The objective of this study was to assess the efficacy and safety of IKERVIS 0.05% and 0.1%, administered once daily, compared to vehicle for the treatment of the signs and symptoms of DED after a 3-month treatment period.

Study (SICCANOVE) NVG06C103 was a Phase III double-masked vehicle controlled randomised multicenter study of IKERVIS 1 mg/ml versus vehicle ***in patients with moderate to severe DED***. The primary objective of the study was to demonstrate the superiority of IKERVIS administered once daily versus vehicle after a 6-month treatment period. The secondary objective was to compare the ocular tolerance and systemic safety of IKERVIS versus vehicle after a 6-month treatment period.

➢***One additional non-randomised open-label, multicentre, one cohort extension clinical study:***

Study (Post-SANSIKA) NVG12D122 was a phase III multicenter, open label, interventional, prospective, non-randomised, one cohort extension study of the previous Phase III study (NVG10E117) to assess the sustainability of the effect of NOVA22007 following treatment discontinuation in improved patients with severe DED. The primary objective of the study is to assess the duration of the improvement following NOVA22007 treatment discontinuation once the patient is markedly improved with respect to the baseline of the main study (at least 2 grades on the modified Oxford scale, i.e. from CFS ≥ 4 to CFS ≤ 2). In total, 67 subjects were included in the study over clinical centres in Europe.

VERKAZIA

Two (2) Clinical Trials (CTs) with VERKAZIA have been conducted in paediatric patients with VKC. The characteristics of the two studies are presented in Table 2.

➢***One pivotal randomised double-masked, multicentre, 3 parallel arms and placebo-controlled clinical study:*** **Study (VEKTIS) NVG09B113** was a phase III, international, multicenter, randomised, double-masked, 3 parallel arms, placebo Controlled study to assess the efficacy and safety of NOVA22007 1 mg/ml (Ciclosporin) eye drops, emulsion administered in Paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis. The primary objective of the study was to compare the efficacy of two different dosing regimens of NOVA22007 versus placebo (vehicle of the formulation) on both the evolution of severe keratitis and the need for rescue medication. In total, 169 subjects were included in the study over clinical centres in Europe (101 patients) and in the rest of the World (68 patients).

➢***One supportive randomised double-masked, multicentre, parallel group and controlled clinical study:***

Study (NOVATIVE) NVG05L101 was a phase II/III international, multicentre, double-masked, randomized, parallel group, dose ranging and controlled study of efficacy and tolerance of NOVA22007 (CsA 0.05% and 0.1%) vs. vehicle in patients with VKC. The primary objective of the study was to assess the efficacy of NOVA22007 0.05% and 0.1%, a CsA cationic emulsion administered four times daily versus vehicle in patients with VKC after a 4-week treatment period. The study was completed on 22 February 2007. In total, 118 patients were included in the study over clinical centres in Europe, in Israel, In Morocco and in Turkey.

Table 2: Key Characteristics of Studies Conducted with VERKAZIA

	Study NVG05L101 (NOVATIVE) Phase II/III	**Study NVG09B113 (VEKTIS) Phase III**
Formulation	BAK formulation	CKC formulation
Status	Completed	Completed
Severity of VKC	No specific requirement Some patients (n=45) had a severe VKC	Severe
Primary objective	Efficacy Primary endpoints: treatment success (overall rating of subjective symptoms) using the BenEzra scale: 1=overall worsening of the subjective findings 2=no change in the symptoms 3=slight improvement with the child still unable to participate in all normal daily activities 4=marked improvement despite temporary mild itching or mucus discharge completely free of all symptoms	Efficacy Composite endpoint at Month 4: - Change in CFS (modified Oxford Scale) - Need for rescue medication (dexamethasone) - Occurrence of corneal ulceration With a penalty-adjusted score: Score at Month X= baseline CFS – Month X baseline + 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 objective	Safety	Safety
Duration	1month + 3 month follow up	4 months + 8 month follow up
Arms	3 arms: – 0.1% NOVA22007 – 0.05% Placebo (vehicle)	3 arms: – NOVA22007 0.1%, one drop twice a day – NOVA22007 0.01, one drop four times a day Placebo (vehicle), one drop four times a day
Dosing regimen	QID four times a day	QID
Nb of patients randomised	118	168
Nb of patients included in SS	118	169

SUMMARY OF ALL CLINICAL STUDIES WITH CICLOSPORIN EYE DROPS

Summary of all clinical studies conducted with CsA 1 mg/mL eye drops emulsion are presented in Table 3.

Table 3: Summary of all clinical studies conducted with CsA 1 mg/mL eye drops emulsion

Study No.	Country	Study type	N	Key Features
Studies in Dry Eye Disease				
Pivotal study				
NVG10E117 (SANSIKA) **Phase III**	Europe	Efficacy and safety	245	A 6-month, multicentre, randomized, double masked, parallel group vehicle controlled study comparing ciclosporin (*CKC formulation)* 0.1% to vehicle + 6 months open label treatment safety follow up One drop QD Patients with severe DED
Supportive studies providing design information for the pivotal Phase III				
N09F0502 **Phase IIa**	France	Safety and Efficacy	53	A 12-week, multicentre, randomized, double-masked, four parallel group, vehicle controlled, dose response study, with ciclosporin *(BAK formulation)* 0.025%, 0.05%, 0.1% and vehicle. One drop BID Sjögren patients with moderate to severe DED
NVG08B112 (ORA) **Phase IIb**	USA	Efficacy and safety	132	A 12-week, multicentre, randomized, double masked, three parallel group, vehicle controlled study with ciclosporin *(CKC formulation)* 0.05%, 0.1% and vehicle One drop QD Patients with mild to moderate DED
NVG06C103 (SICCANOVE) **Phase III**	Europe	Efficacy and safety	492	A 6-month, multicentre, randomized double masked, parallel group vehicle controlled study comparing ciclosporin *(BAK formulation*) 0.1% to vehicle One drop QD Patients with moderate to severe DED
NVG12D122 (Post-Sansika)	Europe	Efficacy and safety	67	A multicenter, open label, interventional, prospective, non-randomized, one cohort extension study to assess the sustainability of the effect of NOVA22007 following treatment discontinuation in improved patients with severe dry eye disease (DED)
Studies in VKC				
Pivotal study				
NVG09B113 (VEKTIS)	Europe, U.S.,Israel and India	Efficacy and safety	169	A Multicenter, Randomized, Double-Masked, 3 Parallel Arms, Placebo Controlled Study to Assess the Efficacy and Safety of NOVA22007 1mg/ml (Ciclosporin/Cyclosporine) eye drops, Emulsion administered in Paediatric Patients with Active Severe Vernal Keratoconjunctivitis with Severe Keratitis
Supportive study				
NVG05L101 (NOVATIVE)	Europe, Israel, Morocco and Turkey	Efficacy and safety	118	A Multicentre, Double-Masked Randomized, Parallel Group, Dose Ranging, Controlled Trial of Efficacy and Tolerance of NOVA22007 (Cyclosporine A (CSA) 0.05% and 0.1% ophthalmic cationic emulsion) versus Vehicle in Patients with Vernal Keratoconjunctivitis

SIII.2 Clinical trial exposure

IKERVIS

All studies (Phase II and Phase III) were randomised, double-masked, vehicle controlled, and conducted for 3 to 6 months with different CsA concentrations (0.025%, 0.05% and 0.1%). In most of the studies (3 out of 4), the posology was 1 drop/once daily, with the exception of the Phase IIa study where patients received 1 drop/twice daily. The pivotal SANSIKA study included a 6-month open label safety follow up.

The similarities of the patient's population were judged sufficient to enable the pooling of safety data to facilitate detection of uncommon ADRs. Therefore, two cohorts i.e. "the Double Masked Cohort" and the "All Studies Cohort" were considered:

- "The Double Masked Cohort" includes data from the 6 month double masked period of the 2 Phase III studies allowing the comparison of the extent of safety issues for IKERVIS 1mg/ml versus the vehicle

- The "All Studies Cohort" include all patients who received one drop once daily of IKERVIS 1mg/ml (and up to 12 months) at any time during:
  - The 2 Phase III studies (SICCANOVE and SANSIKA); e.g. the double masked period plus the 6-month open period where patients from the vehicle group after 6 months were switched to and received IKERVIS 1 mg/ml;

  - The phase IIb study (ORA - NVG08B112).

It should be noted that:

- The Phase IIa study was not included in this cohort due to the use of a different dose regimen (BID).

- Also Post-SANSIKA study NVG12D122 (phase III) which was an extension study of the previous Phase III study (NVG10E117) is presented separately (see Table 12).

IKERVIS patient exposure (excluding the supportive study, Post-SANSIKA NVG12D122) is displayed in Table 4.

Table 4: IKERVIS patient exposure (all doses) excluding Post-SANSIKA NVG12D122

Study	Indication	Duration Dose	Number of patients				
			0.025%	0.05%	0.1%	Vehicle	Total CsA
N090502 Phase IIa (BAK)	Moderate to severe DED/ Sjögren	3 months 2 drops/day	12	14	12	15	38
NVG08B112 Phase IIb ORA (CKC)	Mild to moderate DED	3 months 1 drops/day	--	44	45	43	89
NVG06C103 Phase III SICCANOVE (BAK)	Moderate to severe DED	6 months 1 drop/day	--	--	242	250	242
		Completed at 6 months	--	--	204	210	
NVG10E117 Phase III SANSIKA (CKC)	Severe DED	6 months 1 drop/day	--	--	154	90	154
		Completed at 6 months	--	--	129	79	
		Completed at 12 months	--	--	114	--	
			--	--	79	--	79
		(+ 6 month OLE) Completed at 6 months	--	--	63	--	
TOTAL			12	58	452	398	602

TOTAL (at 6 months)	--	--	**396**	289	--
TOTAL (at 12 months)	--	--	**114**	--	--

In the Double Masked Cohort (6 months)

- **Extent exposure**

Table 5 below summarises the extent exposure to IKERVIS 1mg/ml during the double masked period.

Table 5: Extent of exposure in the Double Masked Cohort

Extent of exposure	**NOVA22007 0.1% N=396**		**Vehicle N=340**	
	N	%	N	%
<=1 week	10	2.5	4	1.2
1 to 4 weeks	14	3.5	11	3.2
4 to 14 weeks	35	8.8	22	6.5
14 to 32 weeks	336	84.8	301	88.5
32 to 44 weeks	1	0.3	2	0.6
Number of days, mean (SD)	153.9 (49.9)		158.5 (44.8)	

- **Demographics and other patients' characteristics**

Table 6 below summarises the demographic and other characteristics of the patient population.

Table 6: Demographic and other characteristics – "Double Masked Cohort"

Categories of:	**NOVA22007 0.1% N=396**		**Vehicle N=340**		**Total N=736**	
	N	**%**	**N**	**%**	**N**	**%**
Patients with CFS						
Grade 2 or less	85	21.5	95	27.9	180	24.5
Grade 3	114	28.8	113	33.2	227	30.8
Grade 4*	197	49.7	132	38.8	329	44.7
*One patient had a CFS grade 5 at baseline and was included in this subgroup.						
Sjögren syndrome						
No	250	63.1	217	63.8	467	63.5
Yes	146	36.9	123	36.2	269	36.5
Sex						
Male	65	16.4	48	14.1	113	15.4
Female	331	83.6	292	85.9	623	84.6
Post menopausal status						
No	96	29.0	80	27.4	176	28.3
Yes	235	71.0	212	72.6	447	71.7
Age (years)						
Mean	58.6		59.5		59.0	
SD	13.2	-	12.6		12.9	
Minimum	20		21		20	
Median	60		61		60	
Maximum	90		87		90	
<65	266	67.2	215	63.2	481	65.4
65-74	91	23.0	88	25.9	179	24.3
75-84	32	8.1	34	10.0	66	9.0
>=85	7	1.8	3	0.9	10	1.4
Time since diagnosis (years)						
Mean	7.8		8.4		8.1	
SD	7.0		8.0		7.5	
Minimum	0.1		0.0		0.0	
Median	5.5		6.0		5.8	
Maximum	38.3		64.1		64.1	
For postmenopausal status, percentages were calculated based on female patients.						

In the All Studies Cohort (up to 12 months)

- **Extent of exposure**

Table 7 below summarizes the extent exposure to IKERVIS 1mg/ml, one drop once daily in the "All Studies Cohort" to 12 months. Five hundred and twenty (520) patients were exposed to IKERVIS 1ml/ml one drop once daily for a mean exposure of 191.5 ± 106.3 days.

Table 7: Extent of exposure in "all studies cohort"

Extent of exposure	**NOVA22007 0.1% N=520**	
	N	%
<=1 week	11	2.5
1 to 4 weeks	20	3.8
4 to 14 weeks	83	15.8
14 to 32 weeks	280	53.8
32 to 44 weeks	7	1.3
44 to 52 weeks	71	13.7
>52 weeks	47	9.0
Number of days, mean (SD)	191.5 (106.3)	

- **Demographics and other patients' characteristics**

Table 8 below summarizes the demographic and other characteristics of the patients in the "All Studies Cohort".

Table 8: Demographic and other characteristics - "All Studies Cohort"

Categories of:	**NOVA22007 0.1% N=520**		**Vehicle N=383**		**Total N=903**	
	N	%	N	%	N	%
Patients with CFS						
Grade 2 or less	117	22.5	127	33.2	244	27.0
Grade 3	125	24.0	123	32.1	248	27.5
Grade 4 and 5	278	53.5	133	34.7	411	45.5
Sjögren syndrome						
No	340	65.4	260	67.9	600	66.4
Yes	180	34.6	123	32.1	303	33.6
Sex						
Male	81	15.6	61	15.9	142	15.7
Female	439	84.4	322	84.1	761	84.3
Post menopausal status						
No	126	28.7	90	28.0	216	28.4
Yes	313	71.3	232	72.0	545	71.6
Age (years)						
Mean	59.3		59.6		59.4	
SD	13.3		12.8		13.0	
Minimum	20		21		20	
Median	60		61		60	
Maximum	91		87		91	
<65	337	64.8	241	62.9	578	64.0
65-74	121	23.3	97	25.3	218	24.1
75-84	52	10.0	42	11.0	94	10.4
>=85	10	1.9	3	0.8	13	1.4
Time since diagnosis (years)						
Mean	8.0		8.6		8.3	
SD	6.7		8.1		7.3	
Minimum	0.1		0.0		0.0	
Median	6.2		6.0		6.1	

Categories of:	NOVA22007 0.1% N=520		Vehicle N=383		Total N=903	
	N	%	N	%	N	%
Maximum	38.3		64.1		64.1	
For post-menopausal status, percentages were calculated based on female patients. Patients receiving NOVA22007 in Vehicle/NOVA22007 group of NVG10E117 (Open phase) study were included in NOVA22007 0.1% group.						

In the Phase II studies

- **Extent of exposure**

Extent of exposure in the 2 Phase II studies is displayed in Table 9.

The mean (±SD) exposure to IKERVIS in study N09F0502 with different dosages (0.025% 0.05% 0.1%) ranged from 74.7±35.5 days to 81.6±17.8 days versus 85.9±7.4 days in the vehicle group.

The mean (±SD) exposure to IKERVIS in the ORA study (NVG08B112) ranged from 75.5±22.5 days to 83.4±8.5 days versus 83.6±9.4 days in the vehicle group.

Table 9: Extent of exposure - Phase II studies

	Phase IIa study								Phase IIb ORA study					
	NOVA22007 0.025% N=12		NOVA22007 0.05% N=14		NOVA22007 0.1% N=12		Vehicle N=15		NOVA22007 0.05% N=44		NOVA22007 0.1% N=45		Vehicle N=43	
Daily dose	2drops daily		2drops daily		2drops daily		2drops daily		1drop daily		1 drop daily		1 drop daily	
Extent of exposure	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<=1 week	-	-	-	-	2	16.7	-	-	-	-	1	2.2	-	-
1 to 4 weeks	1	8.3	2	14.3	-	-	-	-	-	-	3	6.7	1	2.3
4 to 14 weeks	11	91.7	12	85.7	9	75.0	15	100	44	100	41	91.1	42	97.7
14 to 32 weeks	-	-	-	-	1	8.3	-	-	-	-	-	-	-	-
Number of days, mean (SD)	81.6 (17.8)		75.8 (26.3)		74.7 (35.5)		85.9 (7.4)		83.4 (8.5)		75.5 (22.5)		83.6 (9.4)	

- **Demographics and other patients' characteristics**

The tables below (Table 10 and Table 11) summarize the demographic and baseline characteristics in the Phase II studies.

Table 10: Demographics and other patients' characteristics - the Phase IIa (N09F0502) study

Categories of:	NOVA22007 0.025% N=12		NOVA22007 0.05% N=14		NOVA22007 0.1% N=12		Vehicle N=15		Total N=53	
	N	%	N	%	N	%	N	%	N	%
Patients with CFS										
Grade 2 or less	6	50.0	5	35.7	7	58.3	8	53.3	26	49.1
Grade 3	4	33.3	4	28.6	4	33.3	6	40.0	18	34.0
Grade 4 and 5	2	16.7	5	35.7	1	8.3	1	6.7	9	17.0
Sjögren syndrome										
Yes	12	100.0	14	100.0	12	100.0	15	100.0	53	100.0
Sex										
Male	1	8.3	-	-	1	8.3	3	20.0	5	9.4
Female	11	91.7	14	100.0	11	91.7	12	80.0	48	90.6

Categories of:	NOVA22007 0.025% N=12		NOVA22007 0.05% N=14		NOVA22007 0.1% N=12		Vehicle N=15		Total N=53	
	N	%	N	%	N	%	N	%	N	%
Post menopausal status										
Yes	9	81.8	13	92.9	8	72.7	10	83.3	40	83.3
No	2	18.2	1	7.1	3	27.3	2	16.7	8	16.7
Age (years)										
Mean	55.9	-	60.8	-	57.2	-	60.5	-	58.8	-
SD	11.3	-	10.2	-	10.8	-	7.5	-	9.8	-
Minimum	31	-	36	-	39	-	46	-	31	-
Median	58	-	64	-	59	-	60	-	60	-
Maximum	70	-	75	-	75	-	74	-	75	-
<65	9	75.0	7	50.0	10	83.3	12	80.0	38	71.7
65-74	3	25.0	6	42.9	1	8.3	3	20.0	13	24.5
75-84			1	7.1	1	8.3	-	-	2	3.8
Time since diagnosis (years)										
Mean	11.4	-	16.0	-	11.3	-	10.7	-	12.4	-
SD	6.4	-	12.7	-	13.1	-	7.7	-	10.3	-
Minimum	2.6	-	3.4	-	0.6	-	0.9	-	0.6	-
Median	11.5		10.5		6.9		8.5		9.4	
Maximum	25.4		46.5		45.4		25.4		46.5	
For postmenopausal status, percentages were calculated based on female patients.										

Table 11: Demographic and characteristic - ORA NVG08B112

Categories of:	NOVA22007 0.05% N=44		NOVA22007 0.1% N=45		Vehicle N=43		Total N=132	
	N	%	N	%	N	%	N	%
Patients with CFS								
Grade 2 or less	34	77.3	32	71.1	32	74.4	98	74.2
Grade 3	8	18.2	11	24.4	10	23.3	29	22.0
Grade 4 and 5	2	4.5	2	4.4	1	2.3	5	3.8
Sjögren syndrome								
No	43	97.7	43	95.6	43	100.0	129	97.7
Yes	1	2.3	2	4.4	-	-	3	2.3
Sex								
Male	7	15.9	10	22.2	13	30.2	30	22.7
Female	37	84.1	35	77.8	30	69.8	102	77.3
Post menopausal status								
No	6	16.2	13	37.1	10	33.3	29	28.4
Yes	31	83.8	22	62.9	20	66.7	73	71.6
Age (years)								
Mean	65.3	-	61.2	-	60.5	-	62.3	-
SD	10.9	-	15.5	-	14.4	-	13.8	-
Minimum	34	-	35	-	27	-	27	-
Median	64	-	60	-	60	-	62	-
Maximum	86	-	91	-	84	-	91	-
<65	23	52.3	25	55.6	26	60.5	74	56.1
65-74	11	25.0	9	20.0	9	20.9	29	22.0
75-84	9	20.5	9	20.0	8	18.6	26	19.7
>=85	1	2.3	2	4.4	-	-	3	2.3
Time since diagnosis (years)								
Mean	8.7	-	7.1	-	9.6	-	8.4	-
SD	6.5	-	4.7	-	8.5	-	6.8	-
Minimum	0.3	-	0.1	-	0.2	-	0.1	-
Median	7.2	-	6.4	-	5.8	-	6.5	-
Maximum	38.8	-	20.8	-	33.6	-	38.8	-
For postmenopausal status, percentages were calculated based on female patients.								

As shown in the tables above, the DED patient populations in the 2 Phase II studies were globally similar with regard to their distribution of age and gender. In the 2 studies, the mean age ranged from 56 to 65 years, and patients were predominantly female and post-menopausal. Main difference relates to disease severity. Patient population involved in N09F0502 study had moderate to severe DED with Sjögren

syndrome and in ORA study (NGV08B112), the patient population had a milder disease (grade 2 or less represented 74% of patients).

In the Post-Sansika study (NVG12D122)

- **Demographics and other patients' characteristics**

The tables below (Table 12 and Table 13) summarize the demographic and baseline characteristics in the phase III Post-Sansika study (NVG12D122). In this study 23 patients exposed to IKERVIS eye drops. These patients were already included in the patient exposure number of SANSIKA study.

Table 12: Demographics and other patients' characteristics – Post-Sansika study NVG12D122

	Total
	N=66*
Age (years)	N=66
Mean (SD)	61.11 (12.90)
Median	63.67
Range (min;max)	(24.1-81.1)
Gender	N=66
Female, N (%)	58 (87.9)
Male, N (%)	8 (12.1)

***** One patient (Patient 005-008) was excluded from the 3 Efficacy populations for violating inclusion criterion, but was included in the Safety Population

Table 13: Age of patients – Post-Sansika study NVG12D122

Age of subjects	**Number of Subjects**
In Utero	0
Preterm newborn- gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days – 23 months)	0
Children (2-11 years)	0
Adolescents (12-17 year)	0
Between 18 and 65 years	34
From 65 years to 84 years	33
85 years and over	0

VERKAZIA

Overall patient exposure - NVG09B113 and NVG05L101

The overall patient exposure in the two clinical trials (VEKTIS and NOVATIVE) is presented below in the Table 14. The 4-month and 12-month exposure to VERKAZIA 0.1% at the proposed dose does not reach the recommended numbers in the EMA/ICH E1A guideline (approximately 300 patients for 6 months and 100 for 12 months), which was expected knowing VKC is a rare disease.

Table 14: Safety database (all doses) Novative (NVG05L101) and Vektis (NVG09B113) studies

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)					
			39	--	36	36	75
		Completed at M1					
			34	--	34	--	68
		Completed at M4					
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

The Table 15 below presents the detailed patient exposure for VERKAZIA including all patients having taken at least one dose of NOVA22007 at any time (from 4 months up to 12 months) during the 2 Phase III clinical trials (in the clinical study documentation called "All periods cohort").

It should be noted that the patients were pooled in to two dose groups:

- **The high dose group** includes patients from NOVATIVE and VEKTIS who received VERKAZIA 1mg/mL QID (four times per day);
- **The low dose group** includes NOVATIVE patients who received VERKAZIA 0.5mg/ml QID and VEKTIS patients from who received VERKAZIA 1mg/mL BID (two times per day).

Table 15: Extent of exposure in the "All periods cohort"

Exposure	High dose group (n=135)	Low dose group (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)

Source data: CTD Table 1.6

Overall Demographics and other characteristics - NVG09B113 and NVG05L101

Table 16 below summarizes the overall demographics and other characteristics in the two paediatric clinical studies (VEKTIS and NOVATIVE).

Table 16 (CTD 2.6): Demographic and other characteristics - Overall study period (Population: SS) NVG05L101 and NVG09B113 Study

		High dose regimen (N=135)	Low dose regimen (N=138)	Total (N=273)
Age (years)	n	135	138	273
	Mean	8.9	9.1	9.0
	SD	3.3	3.1	3.2
	Median	8.0	9.0	8.0
	Min, Max	4, 21	4, 17	4, 21
	Children (4-11 years)	105 (77.8)	106 (76.8)	211 (77.3)
	Adolescent (12-18 years)	29 (21.5)	32 (23.2)	61 (22.3)
Sex	Male	110 (81.5)	105 (76.1)	215 (78.8)
	Female	25 (18.5)	33 (23.9)	58 (21.2)
Form of VKC	Limbal	10 (7.4)	7 (5.1)	17 (6.2)
	Tarsal	35 (25.9)	31 (22.5)	66 (24.2)
	Both	90 (66.7)	100 (72.5)	190 (69.6)
Type of VKC	Seasonal	51 (37.8)	48 (34.8)	99 (36.3)
	Perennial	84 (62.2)	90 (65.2)	174 (63.7)
Time since Diagnosis (year)	n	135	138	273
	Mean	3.5	3.5	3.5
	SD	2.5	2.5	2.5
CFS (Baseline)	Grade 2 or less	19 (14.1)	17 (12.3)	36 (13.2)
	Grade 3	17 (12.6)	20 (14.5)	37 (13.6)
	Grade 4	79 (58.5)	87 (63.0)	166 (60.8)
	Grade 5	20 (14.8)	14 (10.1)	34 (12.5)

Note: Patient 076 in NVG05L101: Day and month of birth are missing. They were replaced by the 1st of July for the calculation of age (11 years).
Note: Patients receiving NOVA22007 in 'Placebo-Low dose regimen' and 'Placebo-High dose regimen' groups were included in each active group during Period 2.
Note: CFS= Corneal Fluorescein Staining defining the severity of keratitis

Demographics and other characteristics - NVG09B113 (Vektis Study)

The table below (Table 17) summarizes the demographic characteristics in the pivotal phase III Vektis study (NVG09B113). 23 patients receiving vehicle during the study period I (4 months) changed to NOVA 22007 0.1% in the period II and 25 patients receiving vehicle during the study period I changed to NOVA 22007 0.5% in the study period II. Total number of patients exposed to NOVA22007 was 159.

Table 17 (CTD 2.4): Demographic and other characteristics - Overall study period (Population: SS) NVG09B113 Study

		High dose regimen (N=79)	Low dose regimen (N=80)	Total (N=159)
Age (years)	n	79	80	159
	Mean	8.9	9.5	9.2
	SD	3.3	3.3	3.3
	Median	8.0	9.0	9.0
	Min, Max	4, 17	4, 17	4, 17
	Children (4-11 years)	61 (77.2)	58 (72.5)	119 (74.8)
	Adolescent (12-18 years)	18 (22.8)	22 (27.5)	40 (25.2)
Sex	Male	63 (79.7)	60 (75.0)	123 (77.4)
	Female	16 (20.3)	20 (25.0)	36 (22.6)
Form of VKC	Limbal	10 (12.7)	7 (8.8)	17 (10.7)
	Tarsal	20 (25.3)	17 (21.3)	37 (23.3)

	Both	49 (62.0)	56 (70.0)	105 (66.0)
Type of VKC	Seasonal	39 (49.4)	33 (41.3)	72 (45.3)
	Perennial	40 (50.6)	47 (58.8)	87 (54.7)
Time since Diagnosis (year)	n	79	80	159
	Mean	3.1	3.6	3.4
	SD	2.3	2.9	2.6
CFS (Baseline)	Grade 2 or less	0	1 (1.3)	1 (0.6)
	Grade 4	64 (81.0)	72 (90.0)	136 (85.5)
	Grade 5	15 (19.0)	7 (8.8)	22 (13.8)

Note: Patients receiving NOVA22007 in 'Placebo-Low dose regimen' and 'Placebo-High dose regimen' groups were included in each active group during Period 2.
Note: Note: CFS= Corneal Fluorescein Staining defining the severity of keratitis

Demographics and other characteristics - NVG05L101 (Novative Study)

The table below (Table 18) summarizes the demographic and other characteristics in the phase II/III Novative study (NVG05L101). 17 patients receiving vehicle during the study period I changed to NOVA 22007 0.1% in the period II and 19 patients receiving vehicle during the study period I changed to NOVA 2207 0.5% in the study period II. Total number of patients exposed to NOVA2207 was 114.

Table 18 (CTD 2.2): Demographic and other characteristics - Overall study period (Population: SS) NVG05L101 Study

		High dose regimen (N=56)	Low dose regimen (N=58)	Total (N=114)
Age (years)	n	56	58	114
	Mean	9.0	8.6	8.8
	SD	3.4	2.8	3.1
	Median	8.0	8.0	8.0
	Min, Max	4, 21	4, 15	4, 21
	Children (4-11 years)	44 (78.6)	48 (82.8)	92 (80.7)
	Adolescent (12-18 years)	11 (19.6)	10 (17.2)	21 (18.4)
Sex	Male	47 (83.9)	45 (77.6)	92 (80.7)
	Female	9 (16.1)	13 (22.4)	22 (19.3)
Form of VKC	Tarsal	15 (26.8)	14 (24.1)	29 (25.4)
	Both	41 (73.2)	44 (75.9)	85 (74.6)
Type of VKC	Seasonal	12 (21.4)	15 (25.9)	27 (23.7)
	Perennial	44 (78.6)	43 (74.1)	87 (76.3)
Time since Diagnosis (year)	n	56	58	114
	Mean	4.0	3.3	3.7
	SD	2.7	1.9	2.3
CFS (Baseline)	Grade 2 or less	19 (33.9)	16 (27.6)	35 (30.7)
	Grade 3	17 (30.4)	20 (34.5)	37 (32.5)
	Grade 4	15 (26.8)	15 (25.9)	30 (26.3)
	Grade 5	5 (8.9)	7 (12.1)	12 (10.5)

Note: Patient 076 in NVG05L101: Day and month of birth are missing. They were replaced by the 1st of July for the calculation of age (11 years).
Note: Patients receiving NOVA22007 in 'Placebo-Low dose regimen' and 'Placebo-High dose regimen' groups were included in each active group during Period 2.
Note: Note: CFS= Corneal Fluorescein Staining defining the severity of keratitis

SUMMARY OF CLINICAL TRIAL EXPOSURE FOR IKERVIS AND VERKAZIA

Table 19: The summary of total estimated cumulative patient exposure to ciclosporin during the completed seven (7) clinical trials with IKERVIS and VERKAZIA:

Study name (Number)	Primary objective	Total of randomised patients	Dose of NOVA22007	Number of subjects exposed to NOVA22007
IKERVIS				
Phase IIa (N09F0502)	Safety and tolerability as primary objective	53 Sjögren patients with moderate to severe DED	0.025% 0.05% 0.1%	12 14 12
Phase IIb ORA (NVG08B112)	Dose finding, to test the hypothesis that NOVA2207 is superior to its vehicle, using a CAE	132 Patients with mild to moderate DED	0.05% 0.1%	44 45
Phase III SICCANOVE (NVG06C103)	To compare NOVA22007 to its vehicle	495 Patients with moderate to severe DED	0.1%	242
Phase III SANSIKA (NVG10E117)	To compare the efficacy of NOVA 22007 to its vehicle and assess long-term safety of NOVA22007 over a 12 month period	246 Patients with severe DED	0.1%	233
Phase III Post-SANSIKA (NVG10E117)	To assess the duration of the improvement following NOVA22007 discontinuation once the patient is markedly improved with respect to baseline in the main study, i.e. at least 2 grades on the modified Oxford scale, from CFS ≥ 4 to CFS ≤ 2.	67 Patients with severe DED	0.1%	23*
VERKAZIA				
Phase II/III NOVATIVE (NVG05L101)	To assess the efficacy of NOVA22007 0.05% and 0.1%, a CsA cationic emulsion administered four times daily versus vehicle in patients with VKC after a 4-week treatment period.	118 patients with vernal keratoconjunctivitis	0.1% 0.05%	56 58
Phase III VEKTIS (NVG09B113)	To compare the efficacy of two different dosing regimens of keratitis and the need for rescue medication	169 patients with active severe vernal keratoconjunctivitis with severe keratitis	0.1%	159

*These patients were already calculated in the patient exposure number of SANSIKA study

Part II: Module SIV - Populations not studied in clinical trials

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	31 October 2016
Version number of this RMP Module	3

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

IKERVIS

The main exclusion criteria for IKERVIS clinical trial development programme is discussed below:

Exclusion criteria which will remain as contraindications		
Criteria	**Implications for target population**	**Is it considered to be included as missing information (incl. rationale)?**
Patient with active ocular or peri-ocular infection.	Patients with any active ocular infection (viral, bacterial, fungal or protozoal) that had occurred within 90 days before the screening visit were excluded from the studies. Like other immunosuppressants, ciclosporin predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections often with opportunistic pathogens.	No. It is not reasonable to try to gather more information on this condition since it will remain as a contraindication.
Patients with known hypersensitivity to one of the components of the study medications.	This is a usual contraindication to be included into an SmPC.	No. It is not reasonable to try to gather more information on this condition since it will remain as a contraindication.
Exclusion criteria which are NOT proposed as contraindications		
Criteria	**Implications for target population**	**Is it considered to be included as missing information (incl. rationale)?**
Patients with CFS grade 5 or below 4 on the modified Oxford scale were excluded from SANSIKA.	The pivotal Phase III SANSIKA study targeted only patients with a (severe) keratitis graded 4. However, in the 3 other IKERVIS studies, patients with different DED severity levels received IKERVIS 0.1% at the dose proposed for registration, and without any specific additional safety concern.	No. These patients are not in the scope of the current indication of the product.
Patients with an active rosacea and/or progressive pterygium or with a severe blepharitis and/or Meibomian Gland Disease were excluded.	Patients with mild to moderate blepharitis and/or MGD were allowed to be enrolled provided the treatment was appropriate and not changed during the study. Exclusion of patients with active rosacea and severe blepharitis is relevant as these conditions might	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.

	need higher dosage of CsA and other treatments (i.e. antibiotics)	
Patients with abnormalities of the eye or the nasolachrymal drainage system such as the destruction of conjunctival goblet cells or scarring, trauma, post radiation keratitis, Stevens-Johnson syndrome, corneal ulcer history.	These patients are generally excluded from DED clinical trials.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Patients with concurrent systemic disease not stabilized prior to study entry, such as diabetes, thyroid malfunction, uncontrolled autoimmune disease, systemic infections, systemic hypersensitivity.	These patients are generally excluded from clinical trials since they need specific attention and treatment prior to be considered for inclusion in a clinical trial. In addition, such diseases could confound the response to the studied therapy.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Patients receiving topical CsA (e.g. Restasis), tacrolimus or sirolimus within 90 days or topical corticosteroids, antibiotics, pilocarpine, antihistamines, or BAK preserved IOP lowering medications within 30 days before the screening visit, and during the course of the study.	The exclusion of these ocular medications was relevant, as they could have impacted the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Patients receiving artificial tears other than those provided by the sponsor.	Tear substitutes are often used as a symptomatic treatment by DED patients. Since all patients were on AT and other tear substitutes prior to study enrolment, meaning that they were not well controlled and in need of an appropriate treatment, IKERVIS study protocols allowed patients to use them throughout the studies as background treatment. To standardise the use and also ensure that patients of the vehicle group used the AT if needed, all patients were given the same unpreserved AT by the Sponsor. Whether the dose was capped (as in SICCANOVE) or not (as in SANSIKA), the use of AT was a secondary endpoint. It is expected that when patients will be prescribed IKERVIS 1mg/ml they will also receive AT.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.

	A specific statement has been included in section 4.2 (Posology and Method of administration) of IKERVIS 1mg/ml approved SmPC: *If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 15 minutes apart. IKERVIS should be administered last.*	
Patients receiving concomitant medicinal products with possible influence on the tear film, tear secretion or ocular surface, such as pilocarpine, isotretinoin, tetracyclines, antihistamines, tricyclic antidepressants, anxiolytics, antimuscarinics, beta-blockers, phenothiazine, or corticosteroids unless the dose remained stable throughout the study.	The exclusion of these medications unless the dose remained stable throughout the study, was relevant, as they could have impacted the assessment of the study drug. Of note, some included patients were receiving systemic ciclosporin at a stable dose during the study.	Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Patients wearing contact lenses.	Patients wearing contact lenses were excluded since this is a usual warning while on an eye drop treatment. A specific statement has been included in section 4.4 (Special warnings and precautions for use) of IKERVIS 1mg/ml approved SmPC: *Patients wearing contact lenses have not been studied. Careful monitoring of patients with severe keratitis is recommended. Contact lenses should be removed before instillation of the eye drops at bedtime and may be reinserted at wake-up time.*	Categorising this as missing information does not bring any additional value for the risk management of this product.

VERKAZIA

The main exclusion criteria for VERKAZIA clinical trial development programme is discussed below:

Exclusion criteria which will remain as contraindications		
Criteria	**Implications for target population**	**Is it considered to be included as missing information (incl. rationale)?**
Patient with ocular or peri-ocular active infection.	Patients with any active ocular infection (viral, bacterial, fungal or protozoal) that had occurred within 90 days before the screening visit were excluded from the studies.	No. It is not reasonable to try to gather more information on this condition since it will remain as a contraindication.

	Like other immunosuppressants, ciclosporin predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections often with opportunistic pathogens.	
Patients with known hypersensitivity to one of the components of the study medications.	This is a usual contraindication to be included into an SmPC.	No. It is not reasonable to try to gather more information on this condition since it will remain as a contraindication.
Exclusion criteria which are NOT proposed as contraindications		
Criteria	**Implications for target population**	**Is it considered to be included as missing information (incl. rationale)?**
Any relevant ocular anomaly other than VKC interfering with the ocular surface including trauma, post radiation keratitis, severe blepharitis, rosacea, corneal ulcer etc.	Such anomalies could confound the response to the studied therapy.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Abnormal lid anatomy, abnormalities of the nasolacrimal drainage system or blinking function in either eye.	These patients are generally excluded from ophthalmic clinical trials.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
History of ocular herpes, varicella-zoster or vaccinia virus infection	Such abnormalities could confound the response to the studied therapy.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Any ocular diseases other than VKC requiring topical ocular treatment during the course of the study.	Such diseases and treatments could confound the response to the studied therapy.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Contact lenses wear during the study.	Patients wearing contact lenses were excluded since the usage of contact lenses is a usual warning while on an eye drop treatment.	No. Categorising this as missing information does not bring any additional value for the risk management of this product.
Topical and/or systemic use of corticosteroids within one week prior to enrolment.	The use of such medications could have impacted the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the

		risk management of this product.
Topical ciclosporin (e.g. Restasis®), tacrolimus or sirolimus within 90 days prior to enrolment.	The use of such medications could have impacted the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Scraping of the vernal plaque within one month prior to the baseline visit.	The scraping of the vernal plaque could impact the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Ocular surgery within 6 months prior to the Baseline visit (excluding surgical treatment of the vernal plaque).	The surgery could impact the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Systemic disease not stabilized within 30 days before the Baseline Visit (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections) or judged by the investigator to be incompatible with the study.	These patients are generally excluded from clinical trials since they need specific attention and treatment prior to be considered for inclusion in a clinical trial. In addition, such diseases could confound the response to the studied therapy.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Presence or history of severe systemic allergy.	These patients have increased risk of severe allergic reactions due to the study or procedural medications.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Any intake of systemic immunosuppressant drugs within 90 days before the Baseline Visit.	The use of these medications could have impacted the assessment of the study drug.	No. Categorising this as missing information does not bring any additional value for the risk management of this product.
History of malignancy in the last 5 years.	Malignancy is "important potential risk" for ciclosporin due to its immunosuppressive activity.	No. Categorising this condition as missing information does not bring any additional value for the risk management of this product. The risk of malignancies in or around the eye is further investigated in the VERKAZIA PASS.

Pregnancy or lactation at the baseline Visit.	These patients are generally excluded from clinical trials.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
History of drug addiction or alcohol abuse.	These patients are generally excluded from clinical trials.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Presence or history of any systemic or ocular disorder, condition or disease that could possibly interfere with the conduct of the required study procedures or the interpretation of study results.	These patients are generally excluded from clinical trials to maximise the reliability of study results.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Participation in a clinical trial with an investigational substance within the past 30 days.	These patients are generally excluded from clinical trials.	No. Not relevant for post-marketing phase.
Participation in another clinical study at the same time as the present study.	These patients are generally excluded from clinical trials.	No. Not relevant for post-marketing phase.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

IKERVIS

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

VERKAZIA

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure. In case of VERKAZIA, this is particularly relevant due to orphan indication (limited number of patients included the clinical trial development program) and due to short exposure times in clinical studies. For more information, see SIV3: Children, VERKAZIA.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Children

IKERVIS

DED rarely occurs in children, and DED is even more a heterogeneous disease in children than in adults. Children were not included in the clinical studies with IKERVIS. A product specific waiver (PIP EMEA 000575-PIP01-09 – ema-pip-waver) was granted on February 2010 (EMA decision 118885/2010) (EMEA 2010) for 'all subsets of the paediatric population' with DED, 'from birth to less than 18 years of age on the grounds that IKERVIS does not represent a significant therapeutic benefit as clinical studies(s) are not feasible'.

A specific statement has thus been included in the SmPC section 4.2 (Posology and Method of administration) of IKERVIS 1mg/ml approved SmPC: *There is no relevant use of IKERVIS in children and adolescents aged below 18 in the indication*.

In addition, the following usual statement has been included into SmPC section 5.1 (Pharmacodynamic properties) of IKERVIS 1mg/ml approved SmPC: *The European Medicines Agency has waived the obligation to submit the results of studies with IKERVIS in all subsets of the paediatric population for dry eye disease (see section 4.2 for information on paediatric use).*

VERKAZIA

The targeted patient population of VERKAZIA are children from 4 years of age and adolescents. As part of a Paediatric Investigation Plan approved in July 2009, a pivotal randomised, double-masked, multicentre, 3 parallel arms and placebo-controlled study (NVG09B113 –VEKTIS) has been completed in children from 4 to 18 years old with severe vernal keratoconjuntivitis (VKC). In addition, one supportive randomised double-masked, multicentre, parallel group and controlled clinical study (NOVATIVE) has been completed in 2007 in children from 4 years up.

Like often in clinical development, the long-term safety information from VEKTIS and NOVATIVE studies remains limited due to short exposure times:

- In the VEKTIS study, following the 4-month double masked vehicle controlled period (Period I), patients continued to be followed in an 8-month follow-up (Period II). 143 patients completed Period I. 29 patients received the high dose (4 drops daily) and 25 the low dose (2 drops daily) for 12 months.

- NOVATIVE study had two study periods as well. Period I was a 4-week multicentre, double-masked, randomized, three parallel groups, vehicle – controlled, treatment period. Period II was a 3-month multi-centre, double-masked, two parallel groups, and treatment period.

- In VEKTIS and NOVATIVE studies, total 162 patients received ciclosporin 0.05% or 0.1% eye drops 4 times or 2 times per day for at least 4 months and 90 patients for 12 months.

The long-term safety of VERKAZIA is categorized as a safety concern under "Missing information".

No studies in children under 4 years have been conducted. This is not seen as a relevant limitation for the development programme, because typical onset of VKC is usually between 4 and 7 years of age.

For the systemic absorption of ciclosporin, see below "Patient with hepatic/renal impairment".

Elderly

IKERVIS/VERKAZIA

Elderly patients were included in the studies with IKERVIS. Around 11% of patients exposed to IKERVIS in the clinical trials programme were older than 75 years of age.

Studies with VERKAZIA have been limited to paediatric patients, because the target disease (VKC) generally resolves after puberty, usually around 4 to 10 years after onset (Bielory 2000, Leonardi 2002). The disease is still present in adulthood although it occurs very rarely (0.5% of VKC patients have the disease still in adulthood)(Leonardi 2002).

There is no need to adjust the dose in elderly patients.

Pregnant or lactating women

IKERVIS/VERKAZIA

Pregnant or lactating women were excluded from the IKERVIS and VERKAZIA studies. There are no or a limited amount of data regarding the use of ciclosporin in pregnant women. No study administering a topical ophthalmic formulation of ciclosporin has been conducted. Therefore, IKERVIS 1mg/ml or VERKAZIA 1 mg/ml should not be used during pregnancy unless clearly necessary.

Ciclosporin is known to be excreted in human milk following systemic administration. However excretion in human milk after topical treatment has not been investigated. Although blood levels of ciclosporin are extremely low after topical administration, caution should be exercised when IKERVIS or VERKAZIA is administered to nursing mothers.

Patient with hepatic/renal impairment

IKERVIS/VERKAZIA

Patients with hepatic or renal impairment were not studied during the clinical development. Considering the route of administration and the negligible systemic passage of IKERVIS/VERKAZIA, no special considerations are needed in these populations.

Systemic absorption of ciclosporin was measured in both, VEKTIS and NOVATIVE, studies using a specific high-pressure liquid chromatography-mass spectrometry assay and a central laboratory. The quantification method used was an HPLC-MS/MS assay, which is 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 (ULOQ) of 5 ng/mL.

Detailed laboratory tests were conducted in the VEKTIS (NVG09B113) study to investigate the systemic absorption and effects of ophthalmic ciclosporin in paediatric patients:

ALT, AST and creatinine

There were no clinically relevant changes in alanine transaminase (ALT), aspartate aminotransferase (AST) or creatinine over the 4-month randomized period or the 8-month follow-up period in either treatment group. There was no difference between children and adolescents.

Systemic absorption of ciclosporin

During the 4-month randomized period, the highest proportion of patients with quantifiable CsA amounts was 14 patients (28.0%) in the high dose group at Month 4/Early termination. In the low dose group, there were 6 patients (13.3%) at Month 2. The maximum concentration of CsA in the blood was 0.670 ng/mL in the high-dose group and 0.336 ng/mL in the low dose group. No CsA was found in the blood of placebo patients.

At Month 12/Early termination, quantifiable results were reported for 12 patients (17.6%) in the high dose total group and 5 patients (8.2%) in the low dose total group. The maximum blood levels of CsA after the 4-month randomized period were 0.291 ng/mL in the high dose group and 0.180 ng/mL in the low dose group.

Laboratory tests in NOVATIVE Study (NVG05L101):

ALT, AST and creatinine

The majority of laboratory values were within the normal ranges. Few instances of values that were out of range were recorded in all treatment groups. However, none of these values were clinically significant.

Laboratory values (ALAT; ASAT; creatininemia) and changes in values from Screening to Day 28 were generally similar in all treatment groups. No trends were observed.

Systemic absorption of ciclosporin

Systemic absorption of ciclosporin was measured in the NOVATIVE study (NVG05L101) at Month 1. CsA blood levels were detectable in very few treated patients at completion of one month of treatment: one out of 10 patients treated with NOVA22007 0.05% (CsA blood level of 0.13 ng/ml) and 4 out of 6 patients treated with NOVA22007 0.1%. The highest detectable CsA blood level was 0.33 ng/ml in 1 patient treated with NOVA22007 0.1%. In 6 patients treated with the vehicle, there were no detectable CsA blood levels.

Conclusions: The laboratory data from clinical studies demonstrated that there was some absorption of CsA into the blood during the study, especially in patients receiving the high dose. However, because the amounts of absorbed CsA were very low, the systemic passage is considered negligible.

Patients with other relevant co-morbidity

IKERVIS

Not applicable.

VERKAZIA

Not applicable.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

IKERVIS

IKERVIS is indicated for patients with severe DED, i.e. for those with a severe keratitis that does not improve despite treatment with tear substitutes. This is in line with the population studied in the Phase III pivotal study. However, it is not expected that the safety and efficacy will be different in a population with a less severe disease, as it was shown in IKERVIS studies. Indeed, mild or moderate patients were involved in the 2 Phase II studies and moderate to severe patients in the Phase III supportive SICCANOVE study.

VERKAZIA

VERKAZIA proposed indication is targeting patients with severe VKC. In the study NVG09B113 (VEKTIS) completed in 2016 only patients with severe VKC and severe keratitis were included. In the previous study NVG05L101 (NOVATIVE) there were patients with milder VKC as well. See the inclusion criteria regarding the VKC severity for the two studies below:

Inclusion criteria in study NVG09B113 (VEKTIS):

- 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).

Inclusion criteria in study NVG05L101 (NOVATIVE):

- Patient presenting with active VKC (acute or chronic) needing medical treatment.

- At least the two following signs in at least one eye*:
    - - Presence of giant papillae with a diameter ≥ 1 mm on the upper tarsal conjunctiva; AND
    - - Superficial keratitis;
- At least two of the following ocular symptoms with a score > 2 in at least one eye*: burning/stinging, tearing, itching, pain, sticky eyelids, foreign body sensation, mucus discharge and photophobia;
- Hyperemia score equal to or greater than 2.

In post hoc analyses of the NVG05L101 (NOVATIVE) study data it was noticed that when comparing to the entire study population, patients with severe keratitis (defined as grade 4 and 5 CFS at Baseline using the Oxford scale) treated with NOVA22007 showed greater improvement over vehicle 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 1 month (Amrane 2011).

Overall, the preclinical and clinical testing of NOVA22007 justifies the studies and indication of VERKAZIA to be limited in patients with severe VKC. No harm or specific risk is expected if VERKAZIA is used for patients with mild or moderate VKC.

Part II: Module SV - Post-authorisation experience

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	19 March 2018
Version number of this RMP Module	3

Part II: Module SV Post-authorisation experience

SV.1 Post-authorisation exposure

The below patient exposure estimations are based on sales numbers. No data on post-marketing patient exposure is available from other sources such as post-marketing studies.

IKERVIS

Totally 445 754 monthly doses of IKERVIS (i.e. 30 SDUs) have been sold since the first Marketing Authorisation (MA) for the product was granted on March 19, 2015. The patient years of exposure was calculated by dividing the total sales of monthly packages by the number of packages used by one patient during one year (one patient uses 12 packages, i.e. monthly doses, per year). The estimated cumulative patient exposure from post-marketing experience is 37 146 patient years.

In addition, during temporary use authorisation (ATU) period (i.e. Compassionate use program) of IKERVIS conducted in France from 29 October 2013 to 07 June 2015, 8446 monthly units of IKERVIS were sold, which means 704 patients years of exposure.

PAPILOCK supportive data

PAPILOCK (ciclosporin 1 mg/ml) is an orphan drug approved for VKC in Japan under orphan drug status (MAH: Santen Ltd). For the further background of PAPILOCK, see page 5.

After the PAPILOCK MA approval (11 October 2005), 225 456 monthly units of PAPILOCK have been sold in Japan. The patient years of exposure was calculated as above for IKERVIS; the total sales of monthly doses were divided by the number of packages used by one patient during one year (one patient uses 12 packages, i.e. monthly doses, per year). The estimated cumulative patient exposure for PAPILOCK from post-marketing experience is 18 788 patient years.

Part II: Module SVI - Additional EU requirements for the safety specification

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	19 Oct 2018
Version number of this RMP Module	5

Part II: Module SVI Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

IKERVIS/VERKAZIA

IKERVIS or VERKAZIA does not have any particular effect or characteristics that might increase the potential for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	15 Apr 2019
Version number of this RMP Module	7.1

Part II: Module SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table SVII.1 Summary of safety concerns after the approval of the initial RMP (v. 3.0)

IKERVIS (First approved RMP version: 3.0)

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

VERKAZIA (First approved RMP version 6.0)

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 - Long-term safety

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

The risks not considered important for inclusion in the list of safety concerns in the RMP are presented below separately for IKERVIS and VERKAZIA because there are minor differences in the justifications. Instead of grouping the risks under the reasons for exclusion, they are presented one by one and the key reasons (in line with RMP template by EMA) are presented immediately after each safety concern and followed by the justifications.

IKERVIS

Safety concern:	**Development/exacerbation of ocular/peri-ocular infection**

Key reason(s) for not considering the risk important:

- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers

- Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

Justification(s):

Frequency of ocular/peri-ocular infections based on clinical studies:

IKERVIS:

0.37 [0 ; 0.88]

The frequency of Ocular infections, such as keratitis bacterial and herpes zoster ophthalmic, has been described as "uncommon" in IKERVIS SmPC (section 4.8).

VERKAZIA:

Summary of ocular AEs under SOC infections and infestations in period 1 is presented below. All AEs were assessed as not-related to study medication by the investigator.

Summary of Ocular TEAEs under SOC Infections and infestations - Period 1* (Population: SS)
NVG05L101 and NVG09B113 Study

System Organ Class Preferred Term	High dose regimen (N=96)	Low dose regimen (N=93)	Placebo (N=98)
Infections and infestations	0	1 (1.1%)	2 (2.0%)
Hordeolum	0	1 (1.1%)	1 (1.0%)
Conjunctivitis	0	0	1 (1.0%)

Note: If a subject has more than one AE within PT the subject will be counted only once.
Note: MedDRA Version 19.0.
*Period 1: 0-4 months of treatment when patient number in all regimens was similar and thus the numbers of AEs are combarable

Source: Extracted from CTD Table 7.5

PAPILOCK supportive data:

No cases of ocular/peri-ocular infections have been reported in the interventional clinical trials with PAPILOCK.

Justifications:
Categorizing this risk as an important safety concern does not bring additional value on managing the risk because it can be managed by routine PV activities and risk minimisation measures. Also, the indications of IKERVIS/VERKAZIA predispose the patients to infections so it would be difficult in practice to differentiate a possible local infection caused by ciclosporin from a local infection caused by the indication itself.

Health care professionals are already aware of the risk of immunosuppressive medicines like ciclosporin possibly having an impact on the patient's immune system. Active or suspected ocular or peri-ocular infection is a contraindication for the use of the product. Additionally, the immunosuppressive characteristics of ciclosporin are widely explained product information of Ikervis:

IKERVIS SmPC section 4.3:
'*Contraindication: active or suspected ocular or peri-ocular infection*.'
IKERVIS SmPC section 4.4:
IKERVIS has not been studied in patients with a history of ocular herpes and should therefore be used with caution in such patients.

	<u>Effects on the immune system</u> *Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies. Therefore, regular examination of the eye(s) is recommended, e.g. at least every 6 months, when Ikervis is used for years.* *<u>Combination with other medicinal products that affect the immune system</u>* *Co-administration of IKERVIS with eye drops containing corticosteroids could potentiate the effects of IKERVIS on the immune system (see section 4.5).* **IKERVIS PIL section 2:** **'***Do not use IKERVIS if you have an eye infection'***.**

Safety concern:	**Hypersensitivity (including angioedema)**
Key reason(s) for not considering the risk important:	- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers
Justification(s):	Categorizing this risk as an important safety concern does not bring additional value on managing the risk because it can be managed by routine PV activities and risk minimisation measures. Also further characterisation of the risk would not change the benefit-risk ratio of the product. Health care professionals are already aware of the risk of hypersensitivity in relation to the use of any "external agents" including medicinal products. Also, the hypersensitivity reactions caused by medicinal products are usually easy to detect and treat. Hypersensitivity to ciclosporin or any ingredients of the product is a contraindication for the use of IKERVIS and it has been clearly communicated in the SmPC and PIL. Frequency of hypersensitivity cases cannot be reliably estimated from the available clinical trial data but, based on the data received from clinical studies and post-marketing use, it is very low; - IKERVIS/VERKAZIA: No cases of hypersensitivity have been reported in clinical studies with IKERVIS/VERKAZIA. The number of hypersensitivity reactions reported from post-marketing sources is very low. - PAPILOCK supportive data (until 30 June 2016): No hypersensitivity cases in relation to the use of PAPILOCK have been reported from interventional clinical trials or post-marketing sources.

Safety concern:	**Use in pregnant or lactating women**
Key reason(s) for not considering the risk important:	- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers
Justification(s):	Categorizing this missing information as an important safety concern does not bring additional value on managing the risk because it can be managed by routine PV activities and risk minimisation measures. Also further characterisation of the missing information would not change the benefit-risk ratio of the product. Health care professionals (and widely also patients) are already aware of the need to pay attention on the usage of medications during pregnancy and lactation. No additional risk minimisation measures are needed. The information related to the use of IKERVIS during pregnancy or lactation is clearly stated in the product information as follows: **IKERVIS SmPC section 4.6:**

	There is no data from the use of IKERVIS in pregnant women. *Studies in animals have shown reproductive toxicity following systemic administration of ciclosporin at exposure considered sufficiently in excess of the maximum human exposure indicating little relevance to the clinical use of IKERVIS.* *IKERVIS is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.* *Following oral administration, ciclosporin is excreted in breast milk. There is insufficient information on the effects of ciclosporin in newborns/infants. However, at therapeutic doses of ciclosporin in eye drops, it is unlikely that sufficient amounts would be present in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from IKERVIS therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.* **IKERVIS PIL section 2:** *IKERVIS should not be used if you are pregnant. If you could become pregnant you must use contraception while using this medicine.* *IKERVIS is likely to be present in breast milk in very small amount. If you are breast-feeding talk to your doctor before using this medicine.*

VERKAZIA

Safety concern:	**Development/exacerbation of ocular/peri-ocular infection**
Key reason(s) for not considering the risk important:	- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers - Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated
Justification(s):	Frequency of ocular/peri-ocular infections based on clinical studies: **IKERVIS:** 0.37 [0 ; 0.88] The frequency of Ocular infections, such as keratitis bacterial and herpes zoster ophthalmic, has been described as "uncommon" in IKERVIS SmPC (section 4.8). **VERKAZIA:** Summary of ocular AEs under SOC infections and infestations in period 1 is presented below. All AEs were assessed as not-related to study medication by the investigator.

Summary of Ocular TEAEs under SOC Infections and infestations - Period 1* (Population: SS) NVG05L101 and NVG09B113 Study

System Organ Class Preferred Term	High dose regimen (N=96)	Low dose regimen (N=93)	Placebo (N=98)
Infections and infestations	0	1 (1.1%)	2 (2.0%)
Hordeolum	0	1 (1.1%)	1 (1.0%)
Conjunctivitis	0	0	1 (1.0%)

Note: If a subject has more than one AE within PT the subject will be counted only once.
Note: MedDRA Version 19.0.
*Period 1: 0-4 months of treatment when patient number in all regimens was similar and thus the numbers of AEs are combarable

Source: Extracted from CTD Table 7.5

PAPILOCK supportive data:

No cases of ocular/peri-ocular infections have been reported in the interventional clinical trials with PAPILOCK.

Justifications:

Categorizing this risk as an important safety concern does not bring additional value on managing the risk because it can be managed by routine PV activities and risk minimisation measures. Also, the indications of IKERVIS/VERKAZIA predispose the patients to infections so it is difficult in practice to differentiate a possible local infection caused by ciclosporin from a local infection caused by the indication itself.

Health care professionals are already aware of the risk of immunosuppressive medicines like ciclosporin possibly having an impact on the patient's immune system. Active or suspected ocular or peri-ocular infection is a contraindication for the use of the product. Additionally, the immunosuppressive characteristics of ciclosporin are widely explained product information of Verkazia:

VERKAZIA SmPC section 4.3:
'*Contraindication: active or suspected ocular or peri-ocular infection*.'
VERKAZIA SmPC section 4.4:

	<u>Effects on the immune system</u> *'Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies. Therefore, regular examination of the eye(s) is recommended, e.g. every 3 to 6 months, when Verkazia is used for more than 12 months.* *Verkazia has not been studied in patients with an active orofacial herpes simplex infection, a history of ocular herpes, varicella-zoster, or vaccinia virus infection and should therefore be used with caution in such patients.'* *<u>Concomitant therapy</u>* *Co-administration of Verkazia with eye drops containing corticosteroids may potentiate the effects of Verkazia on the immune system. However, in clinical studies, 18 patients received Verkazia (4 times daily) in co-administration with eye drops containing corticosteroids and no increase in the risk of adverse reactions related to the immune system was identified. Therefore, caution should be exercised when corticosteroids are administered concomitantly with Verkazia. (see section 4.5)* **VERKAZIA PIL section 2:** *'Do not use VERKAZIA if you have an eye infection.'* *'Talk to your doctor or pharmacist before using VERKAZIA if you have had or if you suspect any eye infection'*

Safety concern:	**Hypersensitivity (including angioedema)**
Key reason(s) for not considering the risk important:	- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers
Justification(s):	Categorizing this risk as an important safety concern does not bring additional value on managing the risk because it can be managed by routine PV activities and risk minimisation measures. Also further characterisation of the risk would not change the benefit-risk ratio of the product. Health care professionals are already aware of the risk of hypersensitivity in relation to the use of any "external agents" including medicinal products. Also, the hypersensitivity reactions caused by medicinal products are usually easy to detect and treat. Hypersensitivity to ciclosporin or any ingredients of the product is a contraindication for the use of VERKAZIA and it has been clearly communicated in the SmPC and PIL. Frequency of hypersensitivity cases cannot be reliably estimated from the available clinical trial data but based on the data received from clinical studies and post-marketing use, it is very low; - IKERVIS/VERKAZIA: No cases of hypersensitivity have been reported in clinical studies with IKERVIS/VERKAZIA. The number of hypersensitivity reactions reported from post-marketing sources is very low. - PAPILOCK supportive data (until 30 June 2016): No hypersensitivity cases in relation to the use of PAPILOCK have been reported from interventional clinical trials or post-marketing sources.

Safety concern:	**Use in pregnant or lactating women**
Key reason(s) for not considering the risk important:	- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers

Justification(s):	Categorizing this missing information as an important safety concern does not bring additional value on managing the risk because it can be managed by routine PV activities and risk minimisation measures. Also further characterisation of the missing information would not change the benefit-risk ratio of the product. Health care professionals (and widely also patients) are already aware of the need to pay attention on the usage of medications during pregnancy and lactation. No additional risk minimisation measures are needed. Also, VERKAZIA is indicated for children and adolescents (up to 18 years) meaning that most of the patients using VERKAZIA are not fertile or otherwise in the typical age of having children. The information related to the use of VERKAZIA during pregnancy or lactation is clearly stated in the product information as follows: **VERKAZIA SmPC section 4.6:** *There is no data from the use of VERKAZIA in pregnant women.* *Studies in animals have shown reproductive toxicity following systemic administration of ciclosporin at exposure considered sufficiently in excess of the maximum human exposure indicating little relevance to the clinical use of VERKAZIA.* *VERKAZIA is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.* *Following oral administration, ciclosporin is excreted in breast milk. There is insufficient information on the effects of ciclosporin in newborns/infants. However, at therapeutic doses of ciclosporin in eye drops, it is unlikely that sufficient amounts would be present in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from VERKAZIA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.* **VERKAZIA PIL section 2:** If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. VERKAZIA should not be used if you are pregnant. If you could become pregnant you must use contraception while using this medicine. VERKAZIA is likely to be present in breast milk in very small amounts. If you are breast feeding talk to your doctor before using this medicine.

Safety concern:	**Long-term safety in paediatric population**
Key reason(s) for not considering the risk important:	- Known risk that require no further characterisation and are followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adhered by prescribers - Other reasons justified below
Justification(s):	Categorizing this risk as an important safety concern does not bring additional value on managing the risk because it can be manged by routine PV activities and riks minimisation measures. Ciclosporin has been widely used in clinical practice in Europe since the 80's to treat various populations (including children) with various and serious diseases (e.g., prevention of organ graft rejection and immune diseases), using different modes of administration (oral or IV). In addition, different hospital formulations of topical ciclosporin, as well as commercial preparations such as Optimmune, or RESTASIS marketed in the US have been administered to treat eye disorder

	without generating significant safety issues. The indication of VERKAZIA is very rare orphan disease and thus it is natural that it will take time to gather significant patient exposure data and the long-term safety information in the concerned paediatric population. It is clearly stated in Special warnings and precautions for use (section 4.4) of the SmPC that "Efficacy and safety of Verkazia have not been studied beyond 12 months. Therefore, regular examination of the eye(s) is recommended, e.g. every 3 to 6 months, when Verkazia is used for more than 12 months" with respective information in the PIL. Also, there are recommendations in the section 4.2 of the SmCP to decrease the dose when assessed reasonable; to discontinue the treatment after the signs and symptoms are resolved; and to use the product periodically.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

RMP version 3.0 is the latest approved RMP for IKERVIS and RMP version 6.0 (including less safety concerns) for VERKAZIA. The re-classification of safety concerns is discussed separately for each product comparing the safety concerns between the previous approved RMP and this latest proposed RMP version (7.2). Some safety concerns that had been initially listed for IKERVIS were removed during the MAA procedure of VERKAZIA but they are discussed again below under 'IKERVIS'.

IKERVIS (Latest approved RMP 3.0 vs. Current updated RMP 7.2)

Safety concern:	**Ocular reaction: corneal decompensation**
Action:	Removed from Important potential risks (during VERKAZIA MAA procedure) and not further discussed in the RMP anymore
Justification(s):	One serious case ([redacted]) of severe epithelial erosion of the cornea (MedDRA PT: corneal decompensation) was reported in study NVG06C103 (SICCANOVE). The patient was diagnosed with severe epithelial erosion of the right eye cornea, with the epithelial tissue having a mushy consistency. The patient was treated with gentle abrasion of the corneal surface, and the application of a soft contact lens. The patient also received antibiotic drops and artificial tears. The event was reported to be resolved without sequelae within one month. The SAE was assessed by the investigator to be related to IKERVIS. In close investigation of the safety data during the update of this RMP, it was found out that the event has been initially coded incorrectly. The discussions with the study team clarify and the case narrative clearly states that the patient's diagnosis was "severe epithelial erosion of the cornea" instead of corneal decompensation. The reported term by the investigator was "epithelial decompensation of the cornea" where word "compensation" led to incorrect PT code of corneal decompensation. Epithelial erosion/compensation of the cornea and Corneal decompensation are different conditions because the first one refers to epithelial cells in the front part of the cornea and second one to endothelial cells in the deeper layers of cornea. MedDRA PT Corneal decompensation does not match with the case narrative, with the term reported by the investigator or with the given diagnosis in the description of the event (severe epithelial erosion of the cornea). No MedDRA PT for the term reported by the investigator, "epithelial decompensation of the cornea", is available so correct MedDRA PT according to the diagnosis ("severe epithelial erosion of the cornea") would have been Corneal erosion. No other cases of Corneal decompensation have been received from clinical studies or post-marketing sources for IKERVIS. Corneal decompensation was

	initially categorized as a potential risk for IKERVIS because it was the only SADR in the clinical studies with IKERVIS. There is no other information supporting the categorisation of corneal decompensation as a potential risk for the patient. No cases of corneal decompensation were reported in the clinical trials with PAPILOCK (for the background of PAPILOCK, see page 5). There was one non-serious case of corneal oedema which was assessed to be related to ciclosporin. In post-marketing product-use surveys including 2647 patients, other less severe corneal ADRs such as corneal erosion, corneal ulcer and keratitis were reporter in 34 patients (1.3%). Only two (2) of them were serious (MedDRA PTs: ulcerative keratitis and corneal erosion) and the ADRs had not been reported to lead for corneal decompensation. It is known that corneal diseases/complications (e.g. ulcers and severe keratitis) may lead to corneal decompensation but only few corneal AEs have been reported from clinical studies and they have mainly been mild to moderate from severity. Instead of following corneal decompensation as a potential risk for IKERVIS, Santen will follow the occurrence and nature of all AEs including corneal decompensation and all corneal AEs for IKERVIS (and VERKAZIA) according to the company's routine PV processes, especially signal detection processes. In case any new significant information regarding this matter is received, Santen will put in place the needed actions to ensure the patient safety and re-assess the need to include severe corneal complications in the safety concerns of IKERVIS. Removal of Corneal decompensation from potential risk does not cause changes in the product information because it was not specifically mentioned in the section SmPC sections 4.4 (Warnings and precautions for use) or 4.3. (Contraindications). There were no additional risk minimisation activities for this risk.

Safety concern:	**Medication error**
Action:	Removed from important potential risks (during Verkazia MAA procedure) and not further discussed in the RMP anymore
Justification(s):	IKERVIS has low potential to be administered by incorrect route and it does not have potential for serious harm in case administered by incorrect route. IKERVIS does not have specifically narrow therapeutic area and it does not have high potential for serious harm if administered with an incorrect dose. No specific factor increasing the potential for Medication error with IKERVIS has been identified. The frequency of Medication error reports with IKERVIS from post-marketing sources has been low. Cumulatively one (1) case with MedDRA PT Intercepted Drug prescribing error (and Dizziness) and one (1) case with MedDRA PT Intercepted medication error have been reported. In addition, two (2) invalid cases with MedDRA PTs Drug dispensing error and Drug administration error have been reported. No cases of medication error have occurred during the clinical trial programme of IKERVIS. There are clear instructions in the product information how to use the product. There are also clear instructions for the patients to discard unused emulsion from a single-dose container immediately after instillation. However, it is possible that patients use IKERVIS/VERKAZIA single-dose units intentionally for more than once to make one package to last longer and thus to save money, but such use is categorized as misuse, not as medication error. Only once case of misuse has been reported where patient had been intentionally administering incorrect dose (2 drops instead of 1). No AE was reported in relation to that case. It is also possible that patients unintentionally use one single-dose container for more than once. Intentional or unintentional incorrect use of IKERVIS single dose container could in theory lead to the contamination of the product and to an eye infection. However, Development/exacerbation of ocular/peri-ocular infection is already

	categorised as a potential risk for IKERVIS/VERKAZIA and also misuse/medication errors related to possible eye infections are followed. There is no need to have Medication error (or Misuse) as a separate potential risk the products. Instead of following medication errors as a potential risk for IKERVIS, Santen will follow the occurrence the medication errors and the nature of possible AEs related to them as a routine pharmacovigilance activity and report the findings in the periodic safety update reports (PSURs). In case any new significant information regarding this matter is received (e.g. new safety signal is identified), Santen will put in place the needed actions to ensure the patient safety and re-assess the need to include medication errors in the safety concerns of IKERVIS. Removal of Medication error from potential risks does not cause changes in the product nformation because it was not mentioned there (instructions for correct use will remain as they are). There were no additional risk minimisation activities for this risk.

Safety concern:	**Off label use**
Action:	Removed from important potential risks and not further discussed in the RMP anymore
Justification(s):	Off label use is removed from the safety concerns in the RMP version 6.0 based on feedback (D120) from CHMP received during Verkazia centralized MAA procedure. According to the feedback, the potential for the risk is acknowledged. However, the CHMP considered that it does not meet the criteria for being considered as "Important" and shall be therefore removed from the safety concerns. The feedback was agreed by Santen because no ADR(s) has been associated to the off-label use of IKERVIS.

Safety concern:	**Development/exacerbation of ocular/peri-ocular infection**
Action:	Re-classified from Important potential risks to Risks not considered important for inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

Safety concern:	**Hypersensitivity (including angioedema)**
Action:	Re-classified from Important potential risks to Risks not considered important for inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

Safety concern:	**Use in pregnant or lactating women**
Action:	Re-classified from Important missing information to Risks not considered important for inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

VERKAZIA (Latest approved RMP 6.0 vs. Current updated RMP 7.2)

Safety concern:	**Development/exacerbation of ocular/peri-ocular infection**
Action:	Re-classified from Important potential risks to Risks not considered important for

	inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

Safety concern:	**Hypersensitivity (including angioedema)**
Action:	Re-classified from Important potential risks to Risks not considered important for inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

Safety concern:	**Use in pregnant or lactating women**
Action:	Re-classified from Important missing information to Risks not considered important for inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

Safety concern:	**Long-term safety in paediatric population**
Action:	Re-classified from Important missing information to Risks not considered important for inclusion in the list of safety concerns in the RMP (SVII .1.1.)
Justification(s):	See justification in 'Risks not considered important for inclusion in the list of safety concerns in the RMP' (SVII.1.1)

SVII.3 Details of important identified, important potential risks and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks

Not applicable

Important potential risks

IKERVIS/VERKAZIA

PERI-OCULAR SKIN CANCER, CONJUNCTIVAL OR CORNEAL NEOPLASIA	
Potential mechanisms	No clear mechanism established with topical use of CsA.
Evidence source(s) and strength of evidence:	The reason to consider peri-ocular skin cancer, conjunctival or corneal neoplasia as potential risk for ophthalmic CsA is based on literature and general knowledge about the characteristics of immunosuppressive medicines, like CsA, mainly in systemic clinical use. CsA ophthalmic formulations (including IKERVIS and hospital formulations in Europe; and RESTASIS in the US) have already been widely used without generating evidence to this potential risk in clinical studies or post-marketing use. There is limited and conflicting information in the literature on the potential of ocular topical CsA when used long-term, to promote the occurrence of skin

	cancers. Many of the studies related to this risk and published in the medical journals have been limited by their design and study population and it is difficult to extrapolate the findings to ophthalmic practice (Durnian 2007). Bohringer in 2008 performed a study in a series of 76 eyes, using CsA 1% and 2% in patients with thygeson's superficial punctate keratitis. Treatment period was quite long, 2.2 ± 2.1 years with a follow up average 5.9 ± 1.9 years. No sign of malignant transformation was observed in slit lamp examination or in brush cytology specimen from conjunctival epithelium. The author concluded conjunctival malignancy is unlikely to be a potential risk though caution should be exercised and more specifically in patients with atopic dermatitis known to involve t-cell immunity in the conjunctiva. In a recent literature review article (Rouimi et. al. 2018), it was concluded that despite plausible pathophysiologic mechanisms, to date there is no evidence of an increased risk of ocular surface neoplasia with the use of topical ocular CsA.
Characterisation of the risk:	The risk is naturally severe but manageable. It is expected to be related to long-term use of ophthalmic ciclosporin (Durnian 2007). Based on the existing data, it can be assumed that possible ADRs, if any, related to this risk would be very rare.
Risk factors and risk groups:	Patients with ocular or peri-ocular malignant/pre-malignant conditions.
Preventability:	Ciclosporin has been in systemic use already for decades and thus there is already plenty of experience about the active substance in general. This supports the preventability of the risk since health care professionals are generally aware that immunosuppressive medicines like ciclosporin may impact on the patient's immune system and affect host defences against malignancies/neoplasia. The risk is mitigated through routine risk minimisation measures like recommending regular examination of eye(s) in long-term use to ensure early detection of possible pre-malignant/malignant changes. For more information about routine risk minimisation measures, see V.1.
Impact on the risk-benefit balance of the product:	This potential risk has no impact on the benefit-risk balance of the product when mitigated as planned through risk minimisation measures. New information about this risk (e.g. results of Verkazia PASS study) is expected to support the characterisation of the risk as an extremely rare risk which has no impact on the risk-benefit balance of the product and can be mitigated through routine risk minimisation measures.
Public health impact:	No absolute incidence rate of AEs related to this is available since this is a potential risk and no reliable evidence is available. The public health impact is expected to be low since AEs related to this risk are expected rarely, if ever. Also the target population is limited to patients with severe eye diseases, DED/VKC, of which VKC is categorized as an orphan disease.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	21 Feb 2019
Version number of this RMP Module	7.0

Part II: Module SVIII 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	Peri-ocular skin cancer, conjunctival or corneal neoplasia
Missing information	None
SAFETY CONCERNS RELATING TO THE PEDIATRIC TARGET POPULATION (i.e. relevant only to VERKAZIA)	
Missing information	None

Part III: Pharmacovigilance Plan

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	02 Sep 2025
Version number of this RMP Module	7.5

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Specific adverse event follow-up questionnaire for Peri-ocular skin cancer, conjunctival or corneal neoplasia adverse events in paediatric patient population with severe VKC:

The purpose of the form is to ensure systematic/structured follow-up of all adverse events related to the safety concern "peri-ocular, skin cancer, conjunctival or corneal neoplasia" reported for VERKAZIA. This is considered important due to the limited patient exposure data in the concerned patient population/indication. With the follow-up form the MAH wants to ensure that as complete data as possible is received to be used also in further assessments (e.g. signal detection, periodic reporting).The follow-up form is provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 Additional pharmacovigilance activities

IKERVIS

Not applicable

VERKAZIA

VERKAZIA PASS PLAN IN EUROPE consists of two phases:

1. **Feasibility study for Verkazia PASS in Europe**

   Rationale and study objectives:

   Feasibility study objective: To evaluate the feasibility of conducting PASS of Verkazia in Europe (i.e. 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).

   Study design:

   Feasibility study will include an epidemiology review and a feasibility assessment of existing data sources in EU-5 (UK, Spain, Italy, France, Germany). It is also important to understand the linkage capabilities between available databases.

   Study population:

   Paediatric patient population

   Milestones:

   Submission of post-authorisation measure (PAM) protocol (MEA001): 16 Nov 2018

   Approval of PAM submission (MEA001): 20 Jan 2020

   Study report submission to EMA: 30 Mar 2021. Assessment Report for the Post-Authorisation Measure MEA 001:24 June 2021

   The assessment report was received with the following conclusion: "At the moment, the MAH can be agreed that the calculated sample sizes required to conduct the PASS exceed the available

number of patients in all databases and only two data sources could identify specifically VKC. The PASS to assess the risk of ocular malignancies after long term use of Verkazia would not be feasible.

2. **Verkazia PASS in Europe (the conduct of this study is conditional, depending on the outcome of the feasibility study)**

   Not applicable as the study was concluded not to be feasible.

VERKAZIA DISPROPORTIONALITY ANALYSIS OF SPONTANEOUSLY REPORTED ADVERSE EVENT DATABASES

A PASS would not be feasible to conduct due to above mentioned reasons. Instead, disproportionality analysis of spontaneously reported adverse event databases, Vigibase from the WHO and FAERS in the USA, would be performed to assess when two cases of ocular cancer of any type are reported to the MAH. These analyses would use standard methods, the frequentist Proportional Reporting ratio and the Bayesian Multi-Item Gamma Poisson Shrinke, which produces Empirical Bayesian Geometric Mean scores. An analysis stratified by age group, with ciclosporin for eye treatment as exposure and all ocular cancers as outcome would be performed. In these analyses, the comparators would be other eye drops and all other drugs in the database. Any disproportionate signal detected would be immediately communicated to the EMA.

III.3 Summary of the Pharmacovigilance Plan

III.3.1 Table of on-going and planned additional Pharmacovigilance activities

IKERVIS

Not applicable

VERKAZIA

Study Status	Summary of objectives	Safety concerns addressed	Milestones
Category 3 Required additional pharmacovigilance activities (by the competent authority)			
FEASIBILITY STUDY FOR VERKAZIA PASS: A feasibility study for a case-control study linked to existing cancer registries (MEA001) Completed	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 local malignancies: Peri-ocular skin cancer, conjunctival or corneal neoplasia	16 Nov 2018: Submission of PAM protocol 20 Jan 2020: Approval of PAM protocol by EMA 30 Mar 2021: Submission of the study report 24 Jun 2021: Assessment Report for the PAM by EMA

Study Status	Summary of objectives	Safety concerns addressed	Milestones
VERKAZIA PASS: A Phase IV case control study linked to existing cancer registries. Cancelled	To quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia for VKC.		The conduct of this study is conditional, depending on the outcome of the feasibility study: the study was concluded not to be feasible.

Part IV: Plans for post-authorisation efficacy studies

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	02 Sep 2025
Version number of this RMP Module	7.5

Part IV: Plans for post-authorisation efficacy studies

IV.1. Post-authorisation efficacy studies by product

IKERVIS

The efficacy of IKERVIS in its target population has been demonstrated in the clinical trials (CTs). However, the CTs by their nature are of limited duration. When completing IKERVIS centralised procedure, the CHMP recommended SANTEN to conduct 'a post-authorisation study to further explore the long-term effects of IKERVIS treatment on symptoms and disease complications'. A PAES with study number #NVG14L127 is planned to address this recommendation.

The PAES was a Phase IIIb, prospective, interventional, multicentre, three-year study designed to explore the long-term evolution of signs and symptoms, and occurrence of complications in DED patients with severe keratitis receiving IKERVIS (1mg/ml ciclosporin) eye drops administered once daily (QD). The period of the study was from 31 May 2019 to 14 July 2023. Final clinical study report (CSR) was submitted in March 2024

VERKAZIA

Not applicable.

IV.2. Summary of post-authorisation efficacy studies

Product	Study	Objectives	Efficacy uncertainities addressed	Status	Date for submission of interim or final reports
IKERVIS	#NVG14L127 IKERVIS	- To evaluate the long-term efficacy of a continuous treatment of IKERVIS® eye drops in adult dry eye disease (DED) patients with severe keratitis on corneal sign and symptoms, and to find the lag time to improvement in symptoms (if any) and time to relapse (if any). - To assess the ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity, and ocular infection) over the three-year study period."	The long-term effects of IKERVIS treatment on symptoms and disease complications'	Completed	Final report: March 2024

Part V: RISK MINIMISATION MEASURES

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	02 Sep 2025
Version number of this RMP Module	7.5

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Safety concern	**Peri-ocular skin cancer, conjunctival or corneal neoplasia**
Objective of the risk minimisation measures	Increase awareness and reduce the potential for this safety concern.
Routine minimisation measures	**IKERVIS:** - **SmPC section 4.3** 'Contraindications: Ocular or peri-ocular malignancies or premalignant conditions and active or suspected ocular or peri-ocular infection.' **SmPC section 4.4:** Effects on the immune system *Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies. Therefore, regular examination of the eye(s) is recommended, e.g. at least every 6 months, when Ikervis is used for years.* Concomitant therapy *Co-administration of Ikervis with eye drops containing corticosteroids could potentiate the effects of Ikervis on the immune system. Therefore, caution should be exercised when corticosteroids are administered concomitantly with Ikervis (see section 4.5).* - **PIL section 2:** *"Do NOT use IKERVIS if you have had or have a cancer in or around your eye."* **VERKAZIA:** - **SmPC section 4.2:** Recommendations to decrease the dose when assessed reasonable; to discontinue the treatment after the signs and symptoms are resolved; and to use the product periodically: "*If signs and symptoms of VKC persist after the end of the season, the treatment can be maintained at the recommended dose or decreased to one drop twice daily once adequate control of signs and symptoms is achieved. Treatment should be discontinued after signs and symptoms are resolved, and reinitiated upon their recurrence (see section 4.4).*" - **SmPC section 4.3:**

	'Contraindications: Ocular or peri-ocular malignancies or premalignant conditions and active or suspected ocular or peri-ocular infection.' - **SmPC section 4.4:** *Effects on the immune system* *Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies. Therefore, regular examination of the eye(s) is recommended, e.g. every 3 to 6 months, when Verkazia is used for more than 12 months.* *Concomitant therapy* *Co-administration of Verkazia with eye drops containing corticosteroids may potentiate the effects of Verkazia on the immune system. However, in clinical studies, 18 patients received Verkazia (4 times daily) in co-administration with eye drops containing corticosteroids and no increase in the risk of adverse reactions related to the immune system was identified. Therefore, caution should be exercised when corticosteroids are administered concomitantly with Verkazia. (see section 4.5).* - **In PIL section 2:** *"Do NOT use VERKAZIA if you have had or have a cancer in or around your eye."* - **Specific follow up form for peri-ocular skin cancer, conjunctival or corneal neoplasia adverse events reported to VERKAZIA**
Additional risk minimisation measure(s)	N/A
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	By following the occurrence of malignancy cases in the post-marketing phase of IKERVIS/VERKAZIA.
Criteria for judging the success of the proposed risk minimisation measure	N/A
Planned dates for the assessment	The assessment will be done periodically according ciclosporin PSUR cycles (6-month period) and the findings will be discussed in the PSURs. In addition, AEs for ciclosporin are assessed in the continuous signal management process to identify possible safety signals to this or any other risk.
Results of effectiveness measurement	Two (2) valid and two (2) invalid cases with PT terms Malignant neoplasm of conjunctiva and Condition aggravated have been received from the same reporter

	(from France) in June 2016. In the cases ophthalmic CsA (possibly IKERVIS) had worsened situation where there was already a conjunctival dysplasia. However, all the four cases are lacking information for sufficient medical assessment. The cases were identified as a potential signal according to Santen signal management procedures and they were discussed in detail in the PSUR #3 for ciclosporin (DLP: 19 Sep 2016). No label changes are suggested based on these cases due to the lack of information regarding these four cases and because the risk is already mentioned in the section 4.4 (Special warnings and precautions for use).
Impact of risk minimisation	The risk minimisation measure (warning in the SmPC) is expected to impact on the treatment practices (e.g. when prescribing IKERVIS for patients with current conjunctival/corneal neoplasia or history of neoplasia in the eye).
Comment	N/A

V.2 Additional risk minimization measures

Not applicable

V.3 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
IDENTIFIED RISKS		
N/A	**N/A**	**N/A**
POTENTIAL RISK(S)		
Peri-ocular skin cancer, conjunctival or corneal neoplasia	IKERVIS: - Proposed text in section 4.3 with corresponding information in PIL. - Proposed text in section 4.4 with corresponding information in PIL. VERKAZIA: - Proposed text in section 4.2 with corresponding information in PIL. - Proposed text in section 4.3 with corresponding information in PIL. - Proposed text in section 4.4 with corresponding information in PIL. - Specific follow up form for peri-ocular skin cancer, conjunctival or corneal	None

	neoplasia adverse events reported to VERKAZIA	
MISSING INFORMATION		
N/A	**N/A**	**N/A**

Part VI: Summary of the risk management plan by product

Active substance	Ciclosporin
Product(s) concerned (brand name(s)):	IKERVIS® 1mg/ml, eye drops, emulsion VERKAZIA® 1mg/ml, eye drops, emulsion
MAH/Applicant name	SANTEN OY

Data lock point for this module	02 Sep 2025
Version number of this RMP Module	7.5

Part VI: Summary of the risk management plan by product

VI.1 Summary of risk management plan for IKERVIS

This summary of the RMP for IKERVIS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of IKERVIS's RMP.

I. The medicine and what is it used for

IKERVIS® 1mg/ml, eye drops, emulsion is authorised for Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes (see SmPC for the full indication). It contains ciclosporin as the active substance and it is given by ocular route.

Further information about the evaluation of IKERVIS®'s benefits can be found in IKERVIS®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/medicines/human/EPAR/ikervis).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of IKERVIS®, together with measures to minimise such risks and the proposed studies for learning more about IKERVIS®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of IKERVIS® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IKERVIS®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Peri-ocular skin cancer, conjunctival or corneal neoplasia
Missing information	None

II.B Summary of important risks

Important potential risks

PERI-OCULAR SKIN CANCER, CONJUNCTIVAL OR CORNEAL NEOPLASIA	
Evidence for linking the risk to the medicine	The reason to consider peri-ocular skin cancer, conjunctival or corneal neoplasia as a potential risk for ophthalmic ciclosporin is based on scarce information available in literature and general knowledge about the characteristics of immunosuppressive medicines, like ciclosporin. Ciclosporin has already been used for decades as a systemic immunosuppressant for the prevention of graft rejection following organ/tissue transplantation. Ophthalmic formulations of ciclosporin (including IKERVIS and hospital formulations in Europe; and a commercial product in the US) have also been widely used without generating evidence to this potential risk in clinical studies or post-marketing use. Additionally, the information available in literature is limited and conflicting and widely related to the systemic use of ciclosporin with significantly higher doses. Thus, there is no evidence that peri-ocular skin cancer, conjunctival or corneal neoplasia would occur in relation to the use of IKERVIS.
Risk factors and risk groups	Patients with local malignant/pre-malignant conditions in or around the eye.
Risk minimisation measures	IKERVIS: - Proposed text in section 4.3 with corresponding information in PIL. - Proposed text in section 4.4 with corresponding information in PIL.
Additional pharmacovigilance activities	N/A

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

IKERVIS PAES:

- A three-year study to explore the long-term evolution of sign and symptoms, and occurrence of complications in Dry Eye Disease patients with severe keratitis receiving IKERVIS® eye drops

Purpose of the study:

- To evaluate the long-term efficacy of a continuous treatment of IKERVIS® (1mg/mL ciclosporin) eye drops in adult dry eye disease (DED) patients with severe keratitis on corneal sign and symptoms, and to find the lag time to improvement in symptoms (if any) and time to relapse (if any).
- To assess the ocular surface complications (defined as corneal ulceration, corneal perforation, loss of visual acuity, and ocular infection) over the three-year study

period."

The period of the study was from 31 May 2019 to 14 July 2023. Final clinical study report (CSR) was submitted in March 2024

II.C.2 Other studies in post-authorisation development plan

Not applicable

Part VI: Summary of the risk management plan by product - VERKAZIA

VI.1 Summary of risk management plan for VERKAZIA

This summary of the RMP for VERKAZIA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VERKAZIA's RMP.

I. The medicine and what is it used for

VERKAZIA® 1mg/ml, eye drops, emulsion is authorised for Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents (see SmPC for the full indication). It contains ciclosporin as the active substance and it is given by ocular route.

Further information about the evaluation of VERKAZIA®'s benefits can be found in VERKAZIA®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/medicines/human/EPAR/verkazia).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

II.A List of important risks and missing information

Important risks of VERKAZIA® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VERKAZIA®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Peri-ocular skin cancer, conjunctival or corneal neoplasia
Missing information	None

II.B Summary of important risks

PERI-OCULAR SKIN CANCER, CONJUNCTIVAL OR CORNEAL NEOPLASIA	
Evidence for linking the risk to the medicine	The reason to consider peri-ocular skin cancer, conjunctival or corneal neoplasia as a potential risk for ophthalmic ciclosporin is based on scarce information available in literature and general knowledge about the characteristics of immunosuppressive medicines, like ciclosporin. Ciclosporin has already been used for decades as a systemic immunosuppressant for the prevention of graft rejection following organ/tissue transplantation. Ophthalmic formulations of

	ciclosporin (including IKERVIS and hospital formulations in Europe; and a commercial product in the US) have also been widely used without generating evidence to this potential risk in clinical studies or post-marketing use. Additionally, the information available in literature is limited and conflicting and widely related to the systemic use of ciclosporin with significantly higher doses. Thus, there is no evidence that peri-ocular skin cancer, conjunctival or corneal neoplasia would occur in relation to the use of VERKAZIA.
Risk factors and risk groups	Patients with local malignant/pre-malignant conditions in or around the eye.
Risk minimisation measures	VERKAZIA: - Proposed text in section 4.2 with corresponding information in PIL. - Proposed text in section 4.3 with corresponding information in PIL. - Proposed text in section 4.4 with corresponding information in PIL. - Specific follow up form for serious ADRs reported to VERKAZIA
Additional pharmacovigilance activities	FEASIBILITY STUDY FOR VERKAZIA PASS: - A feasibility study for a case-control study linked to existing cancer registries - completed - A PASS study was assessed not to be feasible due to limited number of available patients in databases and only two data sources could identify specifically VKC.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Not applicable

II.C.2 Other studies in post-authorisation development plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**
Category 3 Required additional pharmacovigilance activities (by the competent authority)			
FEASIBILITY STUDY FOR VERKAZIA PASS: A feasibility study for a case-control study linked to existing	To understand the data sources and analytic methods available to quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children	Risk of local malignancies: Peri-ocular skin cancer, conjunctival or corneal neoplasia	16 Nov 2018: Submission of PAM protocol 20 Jan 2020: Approval of PAM protocol by EMA 30 Mar 2021: Submission of the study report to EMA 24 Jun 2021: Assessment

cancer registries Completed	treated with Verkazia for VKC.		Report for the PAM by EMA
VERKAZIA PASS: A Phase IV case control study linked to existing cancer registries. Cancelled	To quantify the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia for VKC.		The conduct of this study is conditional, depending on the outcome of the feasibility study: the study was concluded not to be feasible.

Part VII: Annexes

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Annex No

Annex 4: Specific adverse drug event follow-up form

[This is a follow-up form template which can be used as such when sending the follow up (FU) request via e-mail/regular mail or it can be used for making notes when requesting information verbally. However, the questions shall always be presented in user-friendly way so that they are understandable for the responders having different backgrounds. Only questions for which Santen did not previously receive information shall be asked.]

SPECIFIC FOLLOW UP FORM FOR OCULAR NEOPLASM ADVERSE EVENTS REPORTED TO VERKAZIA®

This is a specific follow up form which is used for systemic collection of medically relevant additional information on adverse events related to Peri-ocular skin cancer, conjunctival or corneal neoplasia risk reported to VERKAZIA®. The information will help Santen to understand the relationship between the reported event and medication. The information provided will be kept in confidence and it will not be used for any other purpose than evaluating the safety of VERKAZIA®.

Case ID (provided by Santen):

REPORTER INFORMATION

The person reporting this information is:

☐ Ophthalmologist
☐ Physician – please provide the area of specialization if any:
☐ Pharmacist (MSc or BSc)
☐ Nurse
☐ Other Health Care Professional, please specify:
☐ Consumer or someone reporting on behalf of the Consumer (Non Health Care Professional)

Reporter name:	**Date:**
Phone:	
E-mail:	
Address:	

1) ADDITIONAL INFORMATION ON THE PATIENT AND TREATMENT

❖ Patient Demographics

Gender: ☐ Male ☐ Female

Initials:

Date of birth:

Age or age group:

Country of residence:

❖ For which indication VERKAZIA was prescribed?

☐ Severe Vernal keratoconjunctivis (VKC)
☐ Other - please specify the indication and reason for prescribing VERKAZIA for the concerned indication:

❖ Which form of VKC the patient has?

☐ Tarsal
☐ Limbal
☐ Mixed VKC

❖ **Which type of VKC the patient has?**

☐ Seasonal – the symptoms occur mainly in the spring time
☐ Perennial - the symptoms occur throughout the year

❖ **When was the patient diagnosed with VKC?**

❖ **VERKAZIA treatment**

Product batch number:

Route of administration:

Daily dose:

Treatment start date:

Treatment stop date:

Ongoing: ☐ Yes ☐ No

❖ **Did the patient continue the treatment with VERKAZIA despite of the adverse event?**

☐ Yes → Did the adverse event abate or disappear? ☐ Yes ☐ No ☐ Not known
☐ No → Did the adverse event abate or disappear? ☐ Yes ☐ No ☐ Not known
☐ Not known

❖ **If VERKAZIA treatment was discontinued, did the patient ever re-start the treatment?**

☐ Yes → Did the adverse event re-appear? ☐ Yes ☐ No ☐ Not known
☐ No
☐ Not known

2) MEDICAL AND MEDICATION HISTORY

❖ **Medical history**

Please provide the patient's medical history.

❖ **Medication History**

Please check the applicable category of the drug used/being used.

Drug	Prior or concomitant medication	Indication	Start date	Stop date	On going
	☐Prior ☐Concomitant				☐
	☐Prior ☐Concomitant				☐
	☐Prior ☐Concomitant				☐
	☐Prior ☐Concomitant				☐
	☐Prior ☐Concomitant				☐
	☐Prior ☐Concomitant				☐

❖ **Was the patient having any other ocular or systemic <u>immunosuppressive</u> medications (such as corticosteroids) during or prior the adverse event?**

☐ Yes – please specify product, indication and treatment period
☐ No

3) ADDITIONAL INFORMATION ON THE REPORTED ADVERSE EVENT

❖ **In your assessment was the adverse event causally related to treatment with VERKAZIA? (Only for Health Care Professionals)**

☐ Yes
☐ Possibly but not sure
☐ No
☐ Do not know

❖ **Recovery from the ADR:**

☐ Recovered → **Recovery date:**
☐ Recovering
☐ Recovered with permanent effect, please clarify:
☐ Not recovered
☐ Unknown

❖ **Did the patient get treatment medication for the adverse event?**

❖ **Is this the first time that the patient experienced this or similar health issue?**

☐ Yes
☐ No - please specify when did it happen and did the patient use any medication at that time?

❖ **Is there any medical documentation (e.g. laboratory results, hospitalization documents, statements by a doctor) that Santen could have to assess and document the adverse event?**

☐ Yes – please provide a copy of the documentation
☐ No

❖ **Please provide any other information which could help Santen to understand the relationship between the event and medication:**

❖ **What type of tumour does the patient have?**

a) ☐Benign ☐Malignant

b) ☐Ocular/periocular (please specify type):_____
☐Other (please specify):_____

❖ **Family History (in relation to cancer)**

List one blood relative per line **(Tick the box)**	**If alive, give age**	**If dead, give age at death**	**Did this person ever have cancer?**	**If "yes" specify type of cancer**	**At what age?**
☐Father			☐Yes ☐No		

☐Mother			☐Yes ☐No		
☐Brother or☐ Sister			☐Yes ☐No		
☐Brother or☐ Sister			☐Yes ☐No		
☐Brother or☐ Sister			☐Yes ☐No		
☐Brother or☐ Sister			☐Yes ☐No		

❖ Treatment for tumour reported

Treatment	Start date	Duration
Radiation therapy		
Chemotherapy If yes, specify treatment: 1. 2. 3. 4.		
Other (Please specify):		

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

N/A