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CADTH COMMON DRUG REVIEW

Clinical Review Report

Cyclosporine (VERKAZIA)

(Santen Canada Inc.)

Indication: Treatment of severe vernal keratoconjunctivitis in children from four years of age through adolescence.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
CI	confidence interval
CDR	CADTH Common Drug Review
CFS	corneal fluorescein staining
CHMP	European Committee for Medicinal Products for Human Use
CORD	Canadian Organization for Rare Disorders
DB	double-blind
FAS	full analysis set
HRQoL	health-related quality of life
IOP	intraocular pressure
MCIDLOCF	minimal clinically important difference last observation carried forward
PP	per-protocol
QUICK	Quality of Life in Children with Vernal Keratoconjunctivitis
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
VAS	visual analogue scale
VEKTIS	vernal keratoconjunctivitis study
VKC	vernal keratoconjunctivitis
WDAE	withdrawal due to adverse event

Drug	Cyclosporine 0.1% (Verkazia)
Indication	Treatment of severe vernal keratoconjunctivitis in children from 4 years of age through adolescence.
Reimbursement request	As per indication.
Dosage form(s) and route of administration)/strength(s)	Topical ophthalmic emulsion, 0.1% w/v for intraocular administration.
NOC date	24-12-2018
Manufacturer	Santen Canada Inc.

Executive Summary

Introduction

Vernal keratoconjunctivitis (VKC) is a rare allergic disorder characterized by bilateral ocular surface inflammation with seasonal relapses in children and adolescents. In addition to the classic seasonal presentation, VKC can present as perennial or have a mixed form. Severe forms be sight-threatening; they typically present with a cobblestone-like appearance of the upper tarsal or limbal conjunctiva, intense itching, corneal damage, and mucous discharge. Information on the prevalence of VKC in Canada is limited; the manufacturer reported conducting a survey through the Hospital for Sick Children in Toronto that produced an estimate of 155 cases of severe VKC, which translates to a prevalence of about 0.04 per 10,000 people. No published guidelines exist for the treatment of VKC. The topical ophthalmic drugs commonly used are vasoconstrictors, antihistamines, mast-cell stabilizers, dual-acting drugs, corticosteroids, and immunomodulators (compounded cyclosporine and tacrolimus). None of these drugs has an approved Health Canada indication for the treatment of VKC.

Verkazia is a cyclosporine 0.1% weight by volume topical ophthalmic emulsion indicated for the treatment of severe VKC in children from four years of age through adolescence. The Health Canada–recommended treatment regimen is administration four times daily. However, maintenance therapy can be given twice daily. It is the first drug to receive this indication and has been granted priority review status by Health Canada.

The objective of this CADTH Common Drug Review (CDR) report is to perform a systematic review of the beneficial and harmful effects of 0.1% cyclosporine topical ophthalmic emulsion administered as one drop four times a day for the treatment of severe VKC in children from four years of age through adolescence.

Stakeholder Engagement

Patient Input

One submission was prepared by the Canadian Organization for Rare Disorders, a registered charity. The submission was based on interviews conducted by the organization with four health care professionals (two pediatric ophthalmologists and two optometrists) and on semi-structured interviews conducted with 10 families with children diagnosed with severe VKC.

Parents of children with severe VKC described how symptoms interfered with the children's participation in school, sports, family events, and every aspect of daily living. Parents reported that there was also a heavy impact on the entire family: not just the time spent in care, going to medical appointments, and daily administration of medicines, but also the impact on the family's ability to take part in many social and recreational activities. Parents were universal in wanting a treatment that would reduce any potential long-term harm to their children's eyes while managing the symptoms reliably on a day-to-day basis.

Clinician Input[1]

Chronic treatment is often needed to control VKC. Topical steroids work well, but carry a high side-effect profile. Some patients who require constant or frequent corticosteroids might develop increased intraocular pressure, leading them to require glaucoma management. In addition, not all patients respond to available treatments; and some become refractory to current treatment options.

Commercially available cyclosporine 0.1% will be mainly used as a steroid-sparing drug; initially, it is not anticipated to present a large treatment paradigm shift. However, as accessibility to Health Canada–approved cyclosporine 0.1% increases — and familiarity with patients' response and tolerability to the drug rises among ophthalmologists — cyclosporine 0.1% is likely to become a first-line treatment for patients who present with moderate to severe VKC. In this scenario, steroids would only be prescribed if a patient experienced an adequate response to cyclosporine 0.1%. These potential future uses could present a shift in the treatment paradigm. In addition, commercially available cyclosporine could be prescribed sooner than otherwise prescribed in situations where accessibility to cyclosporine was a challenge.

Newly diagnosed cases of VKC that do not show severe symptoms and signs are likely to benefit from topical antihistamines/mast-cell stabilizers alone, without the need to add cyclosporine 0.1%. The patients best suited to receive cyclosporine 0.1% are likely those with moderate to severe VKC. However, it is difficult to determine a set of distinct characteristics to define the patients who would best respond to cyclosporine 0.1%, given that the expected response would depend on the patient's history of response to previous treatments (including cyclosporine at different doses), symptoms and signs of disease, number and severity of flare-ups, and history of treatment adherence. Clinician examination and judgment are the best way to decide whether a patient would benefit from cyclosporine 0.1%.

An ideal treatment would reduce the severity of the symptoms in a short period of time (ideally within two weeks), address the underlying inflammatory basis of the disease, have minimal risks, and reduce the burden on caregivers (i.e., the parents of affected children). In practice, clinicians would assess the severity and progress of VKC in a patient by taking a history and conducting an eye exam. Items that are commonly assessed include the number of flare-ups, reported subjective severity and persistency of symptoms, conjunctival signs, presence of papillary reaction and/or Horner-Trantas dots, and the extent of corneal involvement. These items are commonly assessed informally; no grading tool or numeric scale is used in practice. Depending on the severity of the conditions, a patient would come for a first reassessment visit within two weeks. A subsequent assessment visit may be arranged within six weeks of the first reassessment visit. A complete resolution of some of

1 This information is based on information provided in draft form by clinical experts consulted by CDR reviewers for the purpose of this review.

the signs of VKC may not take place until three to four months after treatment initiation. Treatment discontinuation can be considered in cases involving lack of response, disease progression, development of ocular infection, or unacceptable side effects.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One double-blind (DB), triple-arm, parallel-group, phase III randomized controlled trial met the criteria for inclusion in the CDR systematic review. The VErnal KeratoconjunctiviTIs Study (VEKTIS) (N = 169) randomized patients aged four years to 18 years with severe VKC in a 1:1:1 ratio to one of two cyclosporine 0.1% arms (administered four times daily or twice daily) or to placebo. Patients received the study treatment for four months, at which point the primary outcome was assessed and an eight-month safety follow-up period began. During this follow-up period, patients randomized to the placebo group were switched to one of the two active treatment groups in a 1:1 ratio (to either of the active arms). The primary objective of the study was to compare the efficacy of two different dosing regimens of cyclosporine 0.1% versus placebo on both the evolution of severe keratitis and the need for rescue medication.

VEKTIS enrolled patients aged four years to 18 years with severe VKC as defined by a set of inclusion criteria that included a diagnosis of VKC consistent with grade 3 or 4 on the Bonini scale and severe keratitis consistent with grade 4 or 5 on the modified Oxford scale. The primary end point of VEKTIS was the average of the four calculated composite efficacy scores at each month. The composite efficacy outcome was the difference from baseline in the corneal fluorescein staining (CFS) score at assessment visit adjusted by penalties based on the use of rescue medication and development of corneal ulcerations. A positive value in the patient composite efficacy score indicates improvement.

Other relevant outcomes reported by VEKTIS included a 100 mm visual analogue scale assessing photophobia, tearing, itching, and mucous discharge; CFS responders, defined as patients with a mean CFS score of 50% or less of the baseline value during the last three months of treatment who did not withdraw for a reason related to treatment, did not experience ulceration, and did not use rescue medication; use of rescue medication; and scores on the Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire, a self-reported questionnaire for measuring health-related quality of life in children from five to 12 years of age with allergic conjunctivitis, keratoconjunctivitis, or both. Outcomes beyond the primary efficacy end point were not adjusted for multiplicity.

Efficacy Results

The primary outcome in VEKTIS showed that cyclosporine 0.1% was statistically significantly better than placebo using both treatment regimens, with a between-group difference of 0.76 in the least squares mean for the four-times-daily treatment versus placebo (95% confidence interval [CI], 0.26 to 1.27, $P = 0.007$) and a between-group difference of 0.67 in the least squares mean for the twice-daily treatment versus placebo (95% CI, 0.16 to 1.18, $P = 0.01$). Subgroup analyses of the primary outcome based on various baseline characteristics were conducted post hoc and have limited statistical inference value. The average of the four visual analogue scale symptoms measurements indicate larger improvement in the four-times-daily treatment regimen group versus placebo

(least squares mean difference: –19.411; 95% CI, –29.307 to –9.515), but no statistically significant difference in the twice-daily treatment regimen group versus placebo (least squares mean difference: –8.355; 95% CI, –18.402 to 1.693). The proportions of responders in the four-times-daily treatment regimen group and twice-daily treatment regimen group were 57.1% and 61.1%, respectively; in comparison, 34.5% of patients in the placebo group met the responder definition. The results of the QUICK questionnaire show that the four-times-daily treatment regimen group consistently achieved a larger magnitude of benefit versus placebo than the twice-daily treatment regimen group.

Harms Results

During the four-month randomized period of VEKTIS, patients in the twice-daily treatment regimen group had the lowest proportion of patients with at least one adverse event (AE) (33.3%). In contrast, the placebo group had a proportion of 39.7% and the four-times-daily treatment regimen group had a proportion of 42.1%. Over the full period of the study (12 months), 58.0%, 54.5%, and 50.0% experienced at least one AE in the four-times-daily regimen, twice-daily regimen, and placebo (switched to either group during follow-up) groups, respectively. During the four-month randomized period, the placebo group had the highest number of withdrawals due to AEs (four patients [6.9%]). The four-times-daily treatment regimen group had three patients withdraw due to AEs (5.3%); no patients withdrew due to AEs in the twice-daily treatment regimen group. While stinging sensation was not explicitly reported, the manufacturer reported that during the DB phase, "instillation site pain" was reported by six patients (10.5%) in the four-times-daily treatment regimen group, by three (5.6%) in the twice-daily treatment regimen group, and by two (3.4%) in the placebo group. There were four different serious AEs. No deaths were reported.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

	VEKTIS (Full Analysis Set)		
	0.1% Cyclosporine 4 Times Daily N = 56	0.1% Cyclosporine 2 Times Daily N = 54	Vehicle (Placebo) N = 56
Penalties-Adjusted Composite Efficacy Score (Primary End Point)[a]			
Average penalties-adjusted CFS score over the 4 months, mean (SD)	2.06 (1.44)	1.93 (1.37)	1.34 (1.22)
Treatment group difference versus control (95% CI)	0.76 (0.26 to 1.27)	0.67 (0.16 to 1.18)	Ref
P value	0.007	0.010	Ref
Average of the 4 VAS Symptoms Measurements[b]			
Baseline, mean (SD)	75.7 (11.2)	72.6 (9.3)	72.7 (9.5)
End-of-treatment time point (4 months), mean (SD)	26.0 (29.8)	36.0 (32.4)	43.4 (27.3)
Treatment group difference versus control (95% CI)	–19.411 (–29.307 to –9.515)	–8.355 (–18.402 to 1.693)	
P value	< 0.001	0.103	
CFS Responder[b]			
Responder rate	32 (57.1%)	33 (61.1%)	20 (34.5%)
OR (95% CI)	2.583 (1.207 to 5.531)	3.486 (1.576 to 7.713)	Ref

	VEKTIS (Full Analysis Set)		
	0.1% Cyclosporine 4 Times Daily N = 56	0.1% Cyclosporine 2 Times Daily N = 54	Vehicle (Placebo) N = 56
P value	0.015	0.004	Ref
Rescue Medication[b]			
Rate of patients with at least 1 use of rescue medication over the study treatment period (4 months) (95% CI)	0.321 (0.203 to 0.460)	0.315 (0.195 to 0.456)	0.534 (0.399 to 0.667)
QUICK Questionnaire[b]			
Symptoms domain			
Baseline, mean (SD)	61.1 (18.8)	59 (17.6)	63.2 (17.6)
End-of-treatment time point (4 months), mean (SD)	27.6 (23.3)	32.4 (26.2)	37.1 (22.5)
Treatment group difference versus control (95% CI)	–8.766 (–16.403 to –1.129)	–3.817 (–11.646 to 4.013)	ref
P value	0.049	0.338	ref
SAEs			
n (%)	2 (3.5)	1 (1.9)	0
Notable Harms			
Ulcerative keratitis	4 (7.0%)	3 (5.6%)	3 (5.2%)
Conjunctivitis	0	0	1 (1.7%)
Stinging, n (%)	0	0	0

CFS = corneal fluorescein staining; CI = confidence interval; OR = odds ratio; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; Ref = reference; SAE = serious adverse event; SD = standard deviation; VAS = visual analogue scale; VEKTIS = vernal keratoconjunctivitis study.

[a] The primary end point analysis was conducted using analysis of covariance (ANCOVA) with treatment as covariate as well as the baseline CFS and the proportion of time potentially spent taking study medication during the VKC season. Adjustment for type I error was done through the Hochberg's procedure for comparing each dose versus placebo.

[b] Outcome not adjusted for multiplicity.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Critical Appraisal

An important limitation to the external validity of VEKTIS is the difficulty in the clinical interpretation of the primary outcome as well as the clinical interpretation of the secondary outcomes that are not adjusted for multiplicity. In the absence of established validity and a minimal clinically important difference in the primary outcome, clinical interpretation of the magnitude of the observed differences between the active treatment groups and placebo group is not possible. Also, given the placebo-based comparison and lack of any indirect comparison, we were not able to extrapolate the results of the treatment difference versus placebo to the comparators of interest identified in the CDR review protocol. VEKTIS provides clinically relevant outcomes in the form of secondary outcomes. However, these outcomes are not adjusted for multiplicity; as such, it is not possible to use statistical inference to apply the results from the study sample to the Canadian patient population.

Results may have been biased in favour of the four-times-daily treatment regimen group due to the imbalance in the discontinuation rate and the use of heterogenous approaches for data imputation. Specifically, the planned imputation method would have simultaneously

used various imputation approaches (worst observation carried forward, best observation carried forward, last observation carried forward, and average of neighbouring observations) based on the reason of missing data. This may have led to worse patient outcomes in the placebo group compared with the four-times-daily treatment regimen group, as more patients withdrew from the placebo group due to lack of efficacy, which would have been imputed with the worst observation carried forward. Sensitivity analysis using observed data only is not sufficient to assess the impact of the data imputation method due to the higher discontinuation rate in the placebo group versus the four-times-daily group. An additional concern is the apparent imbalance in the baseline disease severity, where more severely affected patients were randomized to the four-times-daily treatment regimen. Nonetheless, disease severity was included as a covariate in the analysis, and further analyses exploring the effect of disease severity did not reveal a clear confounding effect.

Indirect Comparisons

No indirect comparisons were identified or submitted by the manufacturer.

Other Relevant Evidence

VEKTIS included an eight-month safety follow-up phase. At the investigator's discretion, patients who had successfully completed the four-month randomized period were allowed to continue receiving the medication regimen they had been assigned to for another eight months. Patients who were randomized to the placebo group were randomized in an manner equal to the four-times-daily and twice-daily cyclosporine 0.1% groups. Since cyclosporine 0.1% was given at the discretion of the investigator during the follow-up phase, three subgroups of patients developed: subgroup A, consisting of patients who stopped the treatment at month 4 and never used it again; subgroup B, consisting of patients who did not stop their treatment at month 4 and continued it daily; and subgroup C, consisting of patients who used the active treatment in an intermittent manner (on as-needed basis).

[redacted]. The number of patients using rescue medication was stable, except for an increase at the end of the follow-up period in subgroup C patients. Finally, the QUICK questionnaire at the end of the follow-up period indicated that improved symptoms were observable only among subgroup B patients. A very small number of patients ended up in subgroup A (patients who never used the drug during the follow-up period); thus, the results focused on the two other subgroups.

However, due to the descriptive nature of the follow-up phase, the lack of a control arm, and the self-selection nature of treatment intake, no conclusions can be drawn about the efficacy data provided.

Conclusions

One DB, phase III RCT met the criteria for inclusion in the CDR systematic review. VEKTIS (N = 169) compared the efficacy of two cyclosporine 0.1% arms (four times daily or twice daily) with placebo, based on the average of four months composite efficacy outcome, each calculated by subtracting the difference in CFS score (using the modified Oxford score), with penalties added for the use of rescue medication and the occurrence of corneal ulceration. Cyclosporine 0.1% was statistically significantly better than placebo using both treatment regimens, with a between-group difference of 0.76 in the least squares mean for the four-times-daily treatment regimen group versus the placebo group (95% CI, 0.26 to 1.27, *P* = 0.007) and a between-group difference of 0.67 in the least squares mean for the twice-daily treatment regimen group versus the placebo group (95% CI, 0.16 to 1.18, *P* = 0.01). However, the clinical significance of these findings remains unknown due to the lack of established minimal clinically important differences (MCIDs). Other concerns for bias in these results include a potential imbalance in patient symptom severity between groups, an imbalance in the discontinuation rate, and insufficient adjustment for bias due to missing data. Secondary outcomes were not adjusted for multiplicity, but have shown results similar in direction to the primary outcome. No conclusion could be drawn with regard to the efficacy results of the follow-up period due to the lack of a control arm. Safety data from the DB and follow-up phases did not demonstrate any notable SAEs.

According to the consulted clinical experts, patients enrolled in VEKTIS were representative of patients they see with severe VKC. The clinical trial settings in VEKTIS may have contributed to the high rates of adherence reported in the trial. However, clinical experts identified adherence as a potential implementation challenge in some patients. The clinical experts consulted for this review believe it is an option for patients who may require prolonged or high-dose exposure to corticosteroids to control the symptoms and signs of VKC.

Introduction

Disease Background

Vernal keratoconjunctivitis (VKC) is a rare allergic disorder in children and adolescents characterized by bilateral ocular surface inflammation with seasonal relapses.[2] In addition to the classic seasonal presentation, VKC can present as perennial or have a mixed form.[2] Severe forms can be sight-threatening; they typically present with a cobblestone-like appearance of the upper tarsal or limbal conjunctiva, intense itching, corneal damage, and mucous discharge.[3] It is estimated that up to 6% of patients develop visual impairment as a direct consequence of VKC complications, including corneal damage, cataracts, and glaucoma.[4] The disease most commonly affects male patients, has a predominantly childhood onset, and self-resolves by adulthood for the majority of patients. Three distinct phenotypes exist: tarsal, limbal, and mixed. These are characterized by different sets of clinical signs and anatomical site involvement.[5] Severe VKC has been reported to negatively affect the patient's and family's quality of life, sometimes imposing significant limitations on common daily activities and school activities. It may also cause a financial burden.[6,7]

A grading system for the severity of VKC was proposed by Bonini et al.[3] The Bonini scale for grading the severity of VKC consists of six main grades:[3]

- Grade 0, quiescent: The disease has been present in the past or recent present, but the patient is free of symptoms. There is no conjunctival hyperemia and no allergic reaction in the cornea. Non-inflamed papillae may be present.
- Grade 1, mild intermittent: Symptoms, such as itching and mild photophobia, are present during the spring season. Symptoms may be present during the day that have short duration and are well tolerated. There is mild hyperemia without corneal involvement. Giant papillae may be present.
- Grade 2A, moderate intermittent: Symptoms are those described in grade 1, but more frequent and disturbing. There may be mild conjunctival secretion and tearing that affect daily activity. Mild to severe papillary reaction and conjunctival hyperemia (without corneal involvement) may be observed.
- Grade 2B, moderate persistent: Conjunctival hyperemia, secretion, and itching are present every day during the season. There may be occasional superficial punctuate keratitis. Mild to severe papillary reaction may be observed.
- Grade 3, severe: Symptoms are present every day. Daily activities are affected by intense itching and photophobia. There is moderate to severe conjunctival hyperemia as well as secretion associated with Horner-Trantas dots. There is superficial punctuate keratitis. Mild to severe conjunctival papillae are common, with injection and swelling.
- Grade 4, very severe: Daily severe itching and photophobia are present, with mucous discharge on the ocular surface and between papillae. Superficial keratopathy or corneal erosions and ulceration are common. Horner-Trantas dots and mild to severe papillary reaction with injection and swelling are present.
- Grade 5, evolution: Symptoms are occasional during seasonal periods. There may be conjunctival papillary reaction, although the cornea is spared. There may be evidence of conjunctival fibrosis on the upper tarsal conjunctiva or at the fornix.

VKC is a rare disease. Information about its prevalence in Canada is limited; the manufacturer reported conducting a survey through the Hospital for Sick Children in Toronto that produced an estimate of 155 cases of severe VKC, which translates to a prevalence of about 0.04 per 10,000 people.[8] In western Europe, VKC is estimated to affect 3.2 per 10,000 people, while VKC with corneal involvement is estimated to affect 0.8 per 10,000 people.[9]

Diagnosis of VKC is largely based on the classic symptoms and signs in patient presentation. According to the clinical experts consulted for this review, in Canada, a patient would commonly be referred to an ophthalmologist by a family physician or an optometrist, where the diagnosis of VKC can be made. According to clinical experts, no official grading scale is used in practice to assign a level of severity to patients suffering from VKC.

Standards of Therapy

No published guidelines exist for the treatment of VKC. However, generally, an escalating step-wise system based on the severity of presentation is considered acceptable.[3] The topical ophthalmic drugs commonly used are from the following classes: vasoconstrictors, antihistamines, mast-cell stabilizers, dual-acting drugs, corticosteroids, and immunomodulators (compounded cyclosporine and tacrolimus).[6] While corticosteroids are known to be effective in controlling the signs and symptoms and resolving inflammation, they are associated with serious complications, including increased intraocular pressure (IOP) requiring glaucoma management. Prior to Health Canada's approval and the commercial availability of 0.1% cyclosporine, access to cyclosporine for the treatment of VKC was limited to compounding or to the commercially available lower concentration 0.05% cyclosporine Restasis, indicated for dry eye.

Drug

Cyclosporine 0.1% topical ophthalmic emulsion is indicated for the treatment of severe VKC in children from four years of age through adolescence. The treatment regimen recommended by Health Canada is administration four times daily. However, maintenance therapy can be given twice daily. Cyclosporine is an immunomodulator that is passively absorbed by
T-lymphocytes, where it prevents the translocation of the nuclear factor of activated T-cells into the nucleus, which stops the release of pro-inflammatory cytokines that are known to activate T-lymphocytes.[8]

The manufacturer is requesting reimbursement as per indication.

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One submission was prepared by the Canadian Organization for Rare Disorders (CORD), a registered charity. CORD advocates on behalf of those with rare disorders and provides support to patient groups. CORD reports that it received no financial payments from any company in the past two years that would indicate a direct or indirect interest in the drug being reviewed.

The submission was based on interviews conducted by CORD with four health care professionals (two pediatric ophthalmologists and two optometrists) and on semi-structured interviews it conducted with 10 patient families who have children diagnosed with severe VKC.

2. Condition-Related Information

Commonly, patients and patients' families described a difficult and frustrating journey until the correct diagnosis was achieved. Patients' journeys usually took them through several visits to various health care professionals and included a few emergency room visits. Frequently, patients were diagnosed with other atopic conditions, including hay fever, asthma, and other allergies.

"I don't know if it would have made any difference if we had gotten to a specialist earlier, but it might have saved us some much anxiety and wasted time not knowing what was wrong."

All parents reported noticing symptoms that included red eyes, puffiness, and a watery fluid or mucous discharge that would often develop into a "crust" overnight. All of the parents said their children complained of itching or irritation (foreign body sensation) in the eyes (under the lids). Parents also noticed what they described as "bumps" on the upper or lower eyelids and on the cornea. The children complained of "blurry" vision and had a tendency to close their eyes, especially in the daytime. In almost all cases, these symptoms were seasonal, first appearing in the spring and generally lasting five to eight months. However, in three cases, the parents reported that the symptoms were present for longer periods, sometimes throughout the year. Pain was also reported as a common symptom experienced by children.

Symptoms interfered with the children's participation in school, sports, family events, and every aspect of daily living. Parents reported a heavy impact on the entire family, not just because of the time spent in care, going to medical appointments, and daily administration of medicines, but also because of the children's inability to take part in many social and recreational activities.

"We don't know any other families with this condition, so we have felt pretty much alone in learning how to deal with this. It's been six years and we finally feel like his eyes are getting better. Maybe he is finally outgrowing this."

3. Current Therapy-Related Information

Until recently, there has been no approved treatment specific to VKC. However, there are treatment guidelines that use "off-label" treatments, the sequencing of which is based on

the severity of the condition and successive failures at earlier-stage therapies. Most of the parents interviewed whose children have been diagnosed for several years reported having experience with almost all of the available therapies (antihistamines, lubricants, mast-cell stabilizers, steroids, and immunosuppressants). Even parents whose children were more recently diagnosed had gone through several treatment regimens, usually taking some drugs sequentially and others concomitantly. None of the patients reported that their children were "symptom-free" — that is, no red eyes, swollen lids, weeping mucus, or ability to tolerate sunlight — while on antihistamines, with or without another drug (e.g., mast-cell stabilizer) in combination. Of the eight patients prescribed steroids, six reported that the steroids were reasonably effective. However, almost all parents expressed concerns about long-term steroid use. Another concern with steroids was the frequent dosing and constant monitoring to get the dosage right.

Eight of the interviewed patient families had experience with cyclosporine A eye drops; one had experience using tacrolimus eyedrops; four specifically recalled using Restasis (0.05%); and the others could not recall the strength of the cyclosporin A formulation used. Six of the parents reported that the clinician had indicated that she or he was increasing the strength of the drug prepared by the pharmacy. One parent said she was told the strength had been increased to 2%. Five out of eight parents were mostly satisfied with the effects of cyclosporine A in managing their children's symptoms, as was the parent whose child was using tacrolimus. None said the red eyes or puffiness were totally gone, but the children were able to take part in social activities and be outdoors. Three of the parents indicated they were "very worried" about increasing the strength of the cyclosporine, though none reported any AEs (other than initial stinging or irritation that dissipated). The drops were, for the most part, well tolerated, although they did have to be administered three to four times a day. All of the patients said that with cyclosporine, they had been able to reduce or completely eliminate the use of steroids. This was "a big relief" for some parents, even though they recognized that the cyclosporine was not risk-free either.

4. Expectations About the Drug Being Reviewed

Parents were universal in wanting a treatment that would reduce any potential long-term harm to their children's eyes while managing the symptoms reliably on a day-to-day basis. Parents had been informed that the condition would get better and likely resolve on its own as the children got older. However, they were not confident that damage sustained when the child was young might not have a permanent impact. Moreover, some said they had been prescribed many different medicines, often without fully understanding how each worked to treat the condition or what they could expect.

Since all parents had experience with steroids and/or immunosuppressants, they expressed their needs relative to these. Specifically, they called for interventions that would:

- immediately reduce symptoms
- prevent symptoms (i.e., could be used prophylactically)
- be risk-free or unlikely to cause long-term negative effects
- require less frequent administration
- replace rather than add to other treatments
- be fully covered by their drug plans.

Seven of the interviewed parents had experience with Verkazia. One reported noticing an immediate improvement: she said her son's eyes were less watery; he could see better;

and he felt there was “less pressure” in the eye. Two other parents said they were hopeful that Verkazia would be more effective at minimizing symptoms and allowing their children more freedom. They found it easier to use (once daily). One parent reported that she was able to reduce her clinic visits to every other month. Another parent reported that there had been no more visits to the emergency room since starting Verkazia, whereas she had been at least twice in the previous year.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). In addition, as part of the cyclosporine 0.1% review, a panel of four clinical experts was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where gaps in the evidence could be addressed by collecting additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place of the drug in therapy (e.g., potential reimbursement conditions). A summary of the panel discussion is presented in this section.

Description of the Current Treatment Paradigm for the Disease

Treatment of severe VKC currently includes the following: lubrication with artificial tears or other preservative-free artificial tears (to rinse away inflammatory mediators on the ocular surface); anti-inflammatory treatments with topical steroids; Restasis (low-dose cyclosporine 0.05%); compounded cyclosporine at higher doses (e.g., 1%) from a compounding pharmacy; tacrolimus 0.03% ointment (off-label use in the eye); topical and oral anti-allergy treatments with over-the-counter antihistamines; management of coexisting meibomian gland dysfunction or blepharitis (using lash or lid margin scrubs, omega-3 fatty acid vitamin supplements, oral doxycycline [not used in children under age eight due to the risk of dental abnormalities]); referral for allergy testing; and the elimination of offending drugs. Treatment may be year-round or seasonal, depending on the patient. Topical treatments are all considered off-label in Canada; they were not originally approved for VKC use, but have been shown over the years to be beneficial in some patients. Cyclosporine and tacrolimus attempt to modify the underlying disease mechanism, whereas the other treatments target the symptoms. However, different patients may respond to different regimens, so it is helpful to have multiple treatments available. Of note, many patients have a decrease in flare-ups after puberty.

Treatment Goals

An ideal treatment would reduce the severity of the symptoms in a short period of time (ideally within two weeks), address the underlying inflammatory basis of the disease, present minimal risks, and reduce the burden on caregivers (i.e., the parents of affected children). Chronic and recurrent bouts of severe ocular surface inflammation from VKC can lead to corneal scarring, conjunctival scarring, meibomian gland dysfunction, severe dry eye, and blepharitis. As such, greatly reducing or eliminating VKC flare-ups is an ideal treatment goal. Topical steroids work well for young children affected by VKC, but carry the risk of IOP elevation, accelerated cataract development, and ocular infection. Thus,

minimizing the use of steroids is a preferred treatment approach. In addition, reducing the total number of treatments needed in a day is desirable because adherence is difficult in the VKC age group.

Unmet Needs

Topical commercial cyclosporine 0.05% (Restasis) is typically not powerful enough to treat VKC. Multiple treatment modalities are required to control the disease process, which can be overwhelming and expensive for patients and their families. Using multiple treatments can also lead to non-compliance. Also, VKC most commonly affects school-age children, and the frequent dosing of medications can make it difficult for them to attend school. Chronic treatment is often needed to control VKC. Topical steroids, which work well, carry a high risk of side effects. Some patients who require constant or frequent corticosteroids might develop increased IOP, leading them to require glaucoma management. In addition, not all patients respond to available treatments, and some become refractory to current treatment options.

Place in Therapy

Currently, cyclosporine is used without a Health Canada indication (as Restasis 0.05% or compounded by a pharmacy) for patients who need continuous high doses of corticosteroids and/or have an IOP response requiring glaucoma management. Based on clinical experience, treatment response to commercially available 0.05% cyclosporine is not encouraging. The drug under review, cyclosporine 0.1%, will replace the compounded cyclosporine and commercially available 0.05% cyclosporine. In essence, commercially available cyclosporine 0.1% will mainly be used a steroid-sparing drug. By itself, this would not present a significant treatment paradigm shift.

However, as Health Canada–approved cyclosporine 0.1% becomes more accessible — and as familiarity with patients' response and tolerability to the drug rises among ophthalmologists — it is likely that cyclosporine 0.1% may become a first-line treatment for patients presenting with moderate to severe VKC, and that steroids would only be prescribed to patients whose response to cyclosporine 0.1% is inadequate. These uses could present a shift in the treatment paradigm. In addition, commercially available cyclosporine could be prescribed sooner than otherwise prescribed in situations where accessibility to cyclosporine is a challenge (e.g., access to a compounding pharmacy or financial challenges in obtaining commercially available 0.05% cyclosporine).

Patient Population

The diagnosis of VKC requires a slit lamp exam performed by an optometrist or ophthalmologist. The condition is not challenging to diagnose in routine clinical practice, as it often has a distinctive history and features. As such, misdiagnosis is unlikely. Newly diagnosed cases that are not showing severe symptoms and signs are likely to benefit from topical antihistamines or mast-cell stabilizers alone, without the need to add cyclosporine 0.1%.

The patients best suited to receive cyclosporine 0.1% are likely those with moderate to severe VKC symptoms. These patients may or may not have responded to other treatments, but need additional medications to keep the disease under control. Based on cyclosporine's mechanism of action, any patient with active VKC and ocular surface inflammation (red eye, photophobia, eye pain, decreased vision) would respond to

treatment with cyclosporine 0.1%. However, it is difficult to determine a set of distinct characteristics to define the patients who would best respond to cyclosporine 0.1%, given that the expected response would depend on the patient's history of response to previous treatments (including cyclosporine at different doses), symptoms and signs of the disease, number and severity of flare-ups, and history of treatment adherence. Clinician examination and judgment are the best way to decide whether a patient would benefit from cyclosporine 0.1%.

Maintenance therapy can be initiated in patients who exhibit a good response to treatment with cyclosporine 0.1%. The approach to treating symptomatic or pre-symptomatic patients varied among panel members. For example, one will not prescribe cyclosporine 0.1% to pre-symptomatic patients until there is more evidence regarding the safety and tolerability of cyclosporine 0.1% in this population; another may initiate treatment with cyclosporine 0.1% before symptoms appear (in an attempt to lessen impending symptoms) in patients who have the seasonal variety of VKC and a history of positive response to cyclosporine 0.1%.

Patients who have an active eye infection or who had a previous adverse reaction to cyclosporine are unlikely to be prescribed cyclosporine 0.1%.

Assessing Response to Treatment

In practice, clinicians would assess the severity and progress of VKC in a patient by taking a history and conducting an eye exam. Items that are commonly assessed include the number of flare-ups, reported subjective severity and persistency of symptoms, conjunctival signs, the presence of papillary reaction and/or Horner-Trantas dots, and the extent of corneal involvement. These items are commonly assessed informally; no grading tool or numeric scale is used in practice.

Depending on the severity of the condition, a patient would come for a first reassessment visit within two weeks; a subsequent assessment visit may be arranged within six weeks of the first reassessment visit. A complete resolution of some of the signs of VKC may not take place until three to four months after treatment initiation.

During reassessment, clinicians would like to see an overall improvement in or resolution of the symptoms and signs of VKC within a few weeks of initiating treatment. Important outcomes to consider when evaluating treatment response include: reduced number of flare-ups, reduced or eliminated need for steroids, improved ability to perform daily living activities, and reduced overall disruption from VKC on the family.

Discontinuing Treatment

Treatment discontinuation can be considered in cases involving lack of response, disease progression, development of ocular infection, or unacceptable side effects (e.g., intolerable burning sensation).

Prescribing Conditions

Cyclosporine 0.1% for the treatment of severe VKC should be prescribed by an ophthalmologist. The expertise and tools necessary to monitor patients' responses are available in hospital outpatient clinics and community ophthalmology clinics.

Clinical Evidence

The clinical evidence included in the review of cyclosporine is presented in three sections. Section 1, the systematic review, includes pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the manufacturer (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes manufacturer-submitted, long-term extension studies and additional relevant studies or evidence considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objective

To perform a systematic review of the beneficial and harmful effects of one drop of cyclosporine topical ophthalmic emulsion 0.1% weight by volume four times a day for the treatment of severe VKC in children from four years of age through adolescence.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada as well as those meeting the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient population	Patients 4 years to 18 years of age with severe VKC Subgroups: • Sex (male or female) • Age groups (children or adolescent) • VKC grade at baseline (grade 1, 2, 3, or 4) • VKC type at baseline (seasonal or perennial) • VKC form at baseline (limbal, tarsal, or mixed) • Concomitant atopic diagnosis (asthma, eczema, urticaria, or multiple atopies)
Intervention	Cyclosporine topical ophthalmic emulsion, 0.1% w/v, 1 drop 4 times a day
Comparators	Monotherapy or combination therapy, including: • Topical antihistamines • Topical mast-cell stabilizers • Topical dual-activity antihistamines/mast-cell stabilizers • Topical steroids • Tacrolimus 0.1% and 0.03%
Outcomes	**Efficacy outcomes:** • HRQoL using a validated scale[a] • Visual function (e.g., acuity, impairment, activities of daily living)[a] • Symptoms measured with a validated scale (e.g., mucous discharge, photophobia, pain, discomfort, irritation, tearing)[a] • Response to treatment • Relapse

	• Improvement in ocular surface damage (as measured by a validated ocular surface staining procedure) • Measurement of possible limitations in daily life (e.g., school productivity, social participation, sports participation)[a] **Harms outcomes:** AEs, SAEs, WDAEs, mortality, ocular morbidity, and notable harms (ocular infections, stinging)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse events; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; VKC = vernal keratoconjunctivitis; WDAE = withdrawal due to adverse event; w/v = weight by volume.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (https://www.cadth.ca/resources/finding-evidence/press).[10]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cyclosporine (Verkazia) and keratoconjunctivitis. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on June 19, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on October 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH checklist, *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters):[11] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional Internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of 474 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

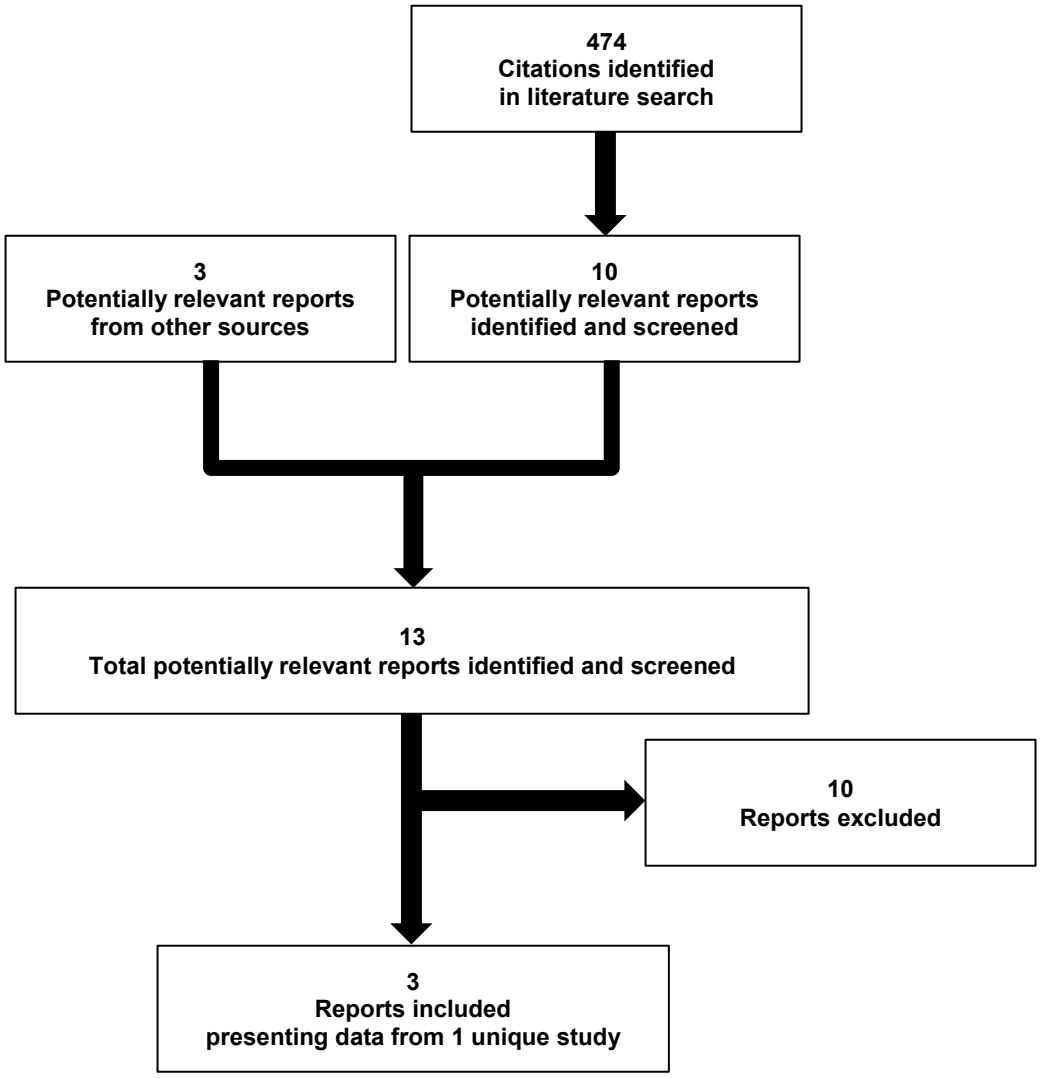


Table 3: Details of Included Studies

		VEKTIS
Designs and Populations	**Study design**	Phase III, multi-centre, randomized, double-masked, 3-arm, parallel, placebo-controlled study
	Locations	Europe, US, India
	Randomized (N)	169
	Inclusion criteria	• 4 years to less than 18 years of age • History of at least one recurrence of VKC in the past year of enrolment • Either not receiving other treatment for VKC or treatment was stopped in accordance with the washout exclusion criteria • Active severe VKC consistent with grade 3 or 4 on the Bonini scale, 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 visual analogue scale
	Exclusion criteria	• Any other ocular anomaly, disease, or object interfering with the ocular surface • Any abnormalities in lid anatomy, nasolacrimal drainage, or blinking function • History of ocular herpes • Active ocular infection • Topical and/or systemic use of corticosteroids within one week prior to enrolment • Topical cyclosporine, tacrolimus, or sirolimus within 90 days prior to enrolment • Scraping of the vernal plaque within one month prior to the baseline visit • Ocular surgery within 6 months prior to the baseline visit • Any systemic disease not stabilized within 30 days prior to the baseline visit • History of severe systemic allergy • Systemic immunosuppressant drugs within 90 days prior to the baseline visit
Drugs	**Intervention**	• Cyclosporine 1 mg/mL 4 times a day (morning, noon, afternoon, and evening), topical ophthalmic application • Cyclosporine 1 mg/mL twice a day (morning and evening) and placebo twice a day (noon and afternoon), topical ophthalmic application
	Comparator(s)	• Placebo 4 times a day (morning, noon, afternoon and evening), topical ophthalmic application
Duration	**Phase**	
	Run-in	Unspecified
	Double-blind	4 months
	Follow-up	8 months
Outcomes	**Primary end point**	Composite efficacy score at 4 months, defined as the mean of the 4 efficacy scores taken at each monthly visit Efficacy was assessed every month during the 4-month treatment period and compared with baseline using a composite criterion based on: • Keratitis as assessed by the modified Oxford scale • Need for rescue medication • Occurrence of corneal ulceration The efficacy score was calculated as: • Patient's score at month X = CFS (baseline) – CFS (month X) + penalty(ies) • Penalty for rescue medication: –1 (per course, with a maximum of 2 courses between 2 scheduled visits) • Penalty for corneal ulceration: –1 (per occurrence)

		VEKTIS
	Other end points	• Use of rescue medication • Keratitis as assessed by the modified Oxford grading scale • Photophobia, tearing, itching, and mucous discharge assessed using a 100 mm visual analogue scale • Responder: defined as a patient with a CFS score at month 4 equal to or smaller than 50% of the baseline CFS score who did not withdraw from the study for a reason possibly due to treatment and who is free from occurrence of ulceration and use of rescue medication in the last 3 months of treatment • QUICK questionnaire
NOTES	**Publications**	Leonardi et al. 2019[12]

CFS = corneal fluorescein staining; DB = double-blind; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; RCT = randomized controlled trial; VEKTIS = Vernal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis.
Note: Two additional reports were included.[13,14]
Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Description of Studies

One double-blind (DB), triple-arm, parallel-group, phase III randomized controlled trial (RCT) was included. The Vernal KeratoconjunctiviTIs Study (VEKTIS) (N = 169), conducted in centres in Europe, the US, and India, randomized patients (1:1:1) to one of two cyclosporine 0.1% arms (administered four times daily or twice daily) or to placebo. Randomization was stratified by country. Patients received treatment for four months, at which point the primary outcome was assessed and an eight-month safety follow-up period began. At that point, patients randomized to the placebo group were switched to one of the two active treatment groups in a 1:1 ratio and continued until they stopped experiencing VKC symptoms or to the end of the study. The primary objective of the study was to compare the efficacy of two different dosing regimens of cyclosporine 0.1% versus placebo on both the evolution of severe keratitis and the need for rescue medication. No screening or run-in periods were reported for VEKTIS.

Populations

Inclusion and Exclusion Criteria

Included patients were between four years and 18 years of age, had had at least one episode of VKC in the year prior to enrolment, and had to meet a severity threshold defined as grade 3 or 4 on the Bonini scale, grade 4 or 5 on the modified Oxford keratitis scale, and a mean score of four subjective symptoms (photophobia, tearing, itching, and mucous discharge) ≥ 60 mm using a 100 mm visual analogue scale (VAS). Patients were excluded if they had received various treatments for VKC within a certain window prior to enrolment. These included topical and/or systemic corticosteroids within one week prior to enrolment; topical cyclosporine, tacrolimus, or sirolimus within 90 days prior to enrolment; and any systemic immunosuppressant drugs within 90 days before the baseline visit. Enrolment was conducted early during the VKC allergy season.

Baseline Characteristics

Included patients were predominantly male (78.6%), Caucasian (70.8%), and between four years and 11 years old (75.5%). These characteristics were balanced across treatment

groups. Similarly, time since diagnosis was balanced across the groups, with a mean ranging from 3.1 years to 3.6 years. Histories of ophthalmic and systemic disorders were also balanced across the three groups. Most enrolled patients had used a treatment for VKC in the past, with the highest proportion in the twice-daily arm (85.3%) and the lowest proportion in the four-times-daily arm (75.0%).

Noticeable imbalances in baseline characteristics were present in disease severity-related measures. The Bonini score at baseline indicated that the placebo group has a less severe disease (the grade 3 proportion in the placebo group was 69.0% versus 59.3% in the twice-daily group and 57.1% in the four-times-daily group), while the CFS score indicated that the four-times-daily treatment regimen group has a more severe disease (the grade 5 proportion in the four-times-daily group was 25.0% versus 9.3% in the twice-daily group and 6.9% in the placebo groups). Table 4 provides a summary of baseline characteristics.

Table 4: Summary of Baseline Characteristics – Full Analysis Set

Title	VEKTIS		
	0.1% Cyclosporine 4 Times Daily (n = 56)	0.1% Cyclosporine 2 Times Daily (n = 54)	Vehicle (Placebo) (n = 58)
Age			
Children 4 years to 11 years, n (%)	43 (76.8%)	38 (70.4%)	46 (79.3%)
Adolescent 12 years to 18 years, n (%)	13 (23.2%)	16 (29.6%)	12 (20.7%)
Mean (SD)	9.1 (3.3)	9.6 (3.4)	8.9 (3.2)
Male, n (%)	44 (78.6%)	42 (77.8%)	46 (79.3%)
Race			
Caucasian, n (%)	40 (71.4%)	38 (70.4%)	41 (70.7%)
Black, n (%)	3 (5.4%)	5 (9.3%)	2 (3.4%)
Asian, n (%)	11 (19.6%)	11 (20.4%)	13 (22.4%)
Other, n (%)	2 (3.6%)	0	2 (3.4%)
Form of VKC			
Limbal, n (%)	8 (14.3%)	2 (3.7%)	7 (12.1%)
Tarsal, n (%)	15 (26.8%)	13 (24.1%)	13 (22.4%)
Both, n (%)	33 (58.9%)	39 (72.2%)	38 (65.5%)
Type of VKC			
Seasonal, n (%)	29 (51.8%)	25 (46.3%)	21 (36.2%)
Perennial, n (%)	27 (48.2%)	29 (53.7%)	37 (63.8%)
Time since diagnosis, years, mean (SD)	3.5 (2.5)	3.6 (2.8)	3.1 (2.6)
Use of prior VKC treatment			
No, n (%)	14 (25.0%)	8 (14.8%)	13 (22.4%)
Yes, n (%)	42 (75.0%)	46 (85.2%)	45 (77.6%)
Eligible eye			
Both eyes, n (%)	28 (50.0%)	35 (64.8%)	34 (58.6%)
Right eye, n (%)	13 (23.2%)	9 (16.7%)	12 (20.7%)
Left eye, n (%)	15 (26.8%)	10 (18.5%)	10(17.2%)
None, n (%)	0	0	2 (3.4%)
Analysis eye			

Title	VEKTIS		
	0.1% Cyclosporine 4 Times Daily (n = 56)	0.1% Cyclosporine 2 Times Daily (n = 54)	Vehicle (Placebo) (n = 58)
Right eye, n (%)	40 (71.4%)	42 (77.8%)	44 (75.9%)
Left eye, n (%)	16 (28.6%)	12 (22.2%)	14(24.1%)
VKC grading (Bonini scale) at baseline (analysis eye)			
Grade 3, n (%)	32 (57.1%)	32 (59.3%)	40 (69.0%)
Grade 4, n (%)	24 (42.9%)	22 (40.7%)	18 (31.0%)
CFS score at baseline			
Grade 4, n (%)	42 (75.0%)	49 (90.7%)	54 (93.1%)
Grade 5, n (%)	14 (25.0%)	5 (9.3%)	4 (6.9%)
History of eye disorders — occurrence in ≥ 1.8% of patients			
Eye disorders, n (%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
History of non-ocular disorders — occurrence in ≥ 5% of patients			
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders, n (%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]
Dermatitis atopic, n (%)	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
History of prior medication — occurrence in ≥ 10% of patients			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

CFS = corneal fluorescein staining; SD = standard deviation; VEKTIS = Vernal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis.
Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Interventions

Patients were randomized following baseline ophthalmological assessments using a computerized randomization schema. Randomization was centralized using an interactive Web response system and stratified by country. Patients were randomized in a 1:1:1 ratio to cyclosporine four times daily, cyclosporine twice daily (with placebo twice daily to maintain blinding), or vehicle (placebo) four times daily. The investigational product was a sterile, ophthalmic, cationic, oil-in-water emulsion containing 1 mg/mL cyclosporine. The vehicle consisted of the same formulation used in the cyclosporine 0.1% treatment arms, excluding the cyclosporine component. The allocation ratio for placebo was split into two groups (ratio: 0.5) to allow equal switching in the second period of the study to one of the two cyclosporine 0.1% dosing regimens. As such, randomization of the placebo patients to the active arms at the beginning of the follow-up period was established at the initial randomization process.

Patients were instructed to instill one drop of study treatment into the lower conjunctival sac of each eye four times daily: in the morning, at noon, in the afternoon, and in the evening. Patients documented their use of the study medication in diaries.

Rescue therapy was available as dexamethasone 0.1% eye drops. Rescue therapy was dispensed in the following situations: worsening keratitis of at least one grade on the modified Oxford scale; no improvement in keratitis during the first two months; symptoms worsening of at least 1 cm on at one of the four symptoms score (photophobia, tearing, itching, or mucous discharge) and worsening or no improvement in the mean of the four symptoms VAS score. Patients were instructed to contact the investigator if VKC signs worsened in order to assess the need for rescue therapy. Patients were instructed to instill one drop in each eye four times daily for five days maximum, and not within 30 minutes before or after using the study medication. A second consecutive course of rescue therapy could be allowed by the investigator after a phone call. Patients could receive a maximum of two consecutive rescue therapies between any two sequentially scheduled visits.

Certain concomitant therapies were prohibited, including artificial tears (except in cases where patients could not reach the investigator for rescue therapy), other topical cyclosporine, tacrolimus, sirolimus, antibiotics, pilocarpine, antihistamines, or any topical ocular treatment other than the study medication. Details on concomitant ophthalmological medications are provided in Table 5.

Table 5: Concomitant Ophthalmological Medications – Occurrence in ≥ 5% of Patients – Four-Month Randomized Period (Safety Set)

Title	VEKTIS		
	0.1% Cyclosporine 4 Times Daily (n = 57)	0.1% Cyclosporine 2 Times Daily (n = 54)	Vehicle (Placebo) (n = 58)
Antihistamines for systemic use, n (%)	[redacted]	[redacted]	[redacted]
Desloratadine, n (%)	7 (12.3%)	6 (11.1%)	5 (8.6%)
Drugs for obstructed airway diseases, n (%)	[redacted]	[redacted]	[redacted]
Salbutamol, n (%)	4 (7.0%)	5 (9.3%)	4 (6.9%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Ophthalmologicals, n (%)	[redacted]	[redacted]	[redacted]
Anti-inflammatory and antirheumatic products, n (%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

VEKTIS = Vernal KeratoconjunctiviTIs Study.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Outcomes

Penalty-Adjusted Composite Efficacy Score

At baseline, a CFS score was assigned to each patient based on the modified Oxford scale. Subsequently, at each monthly assessment visit during the four-month randomization and DB period, a new CFS score was assessed and the need for rescue medication and any occurrence of corneal ulceration were noted. Based on these observations, a composite efficacy score for that particular month's visit was calculated using the following formula:

$$Composite\ efficacy\ score\ at\ month\ X = CFS\ score\ (baseline) - CFS\ \text{score}\ (month\ X) + penalty(ies)$$

A penalty of –1 was assigned when patients used corticosteroids (i.e., rescue medication) or developed corneal ulceration. (A positive value in the patient composite efficacy score indicates improvement.)

The primary end point of VEKTIS is the average of the four calculated composite efficacy scores at each month.

Although the composite end point has not been validated, and no MCID has been established, the provided rationale for using this end point was that it takes into consideration signs (keratitis, as assessed by CFS), symptoms (as rescue therapy would be used for worsening symptoms), and the use of corticosteroids, which are associated with harms in patients with VKC.[8] The European Committee for Medicinal Products for Human Use (CHMP), in its advice to the manufacturer, considered each part of the composite end point to be clinically meaningful and potentially sensitive in detecting an overall treatment effect.[8] CHMP stated that the composite end point could be driven by one of two of the components. For example, corneal ulcers may occur only rarely, as rescue therapy was available.[8] CHMP recommended that the manufacturer increase the maximum duration

allowed for each course of rescue medication or limit the number of courses to ensure the results were not driven by artificially short rescue medication courses. The manufacturer implemented the second recommendation.[8] Additionally, CHMP recommended sensitivity analyses to explore changes in the penalty weighting for rescue therapy, and noted that giving the same weight to the need for rescue therapy as to the occurrence of corneal ulcer appeared to be unjustified.[8]

Visual Analogue Scale

Four VKC symptoms were assessed using a self-administered VAS ranging from 0 mm to 100 mm: photophobia, tearing, itching, and mucous discharge. A decrease in the VAS score from baseline indicated improvement. No validity or MCID was found for the VAS of these symptoms in patients with severe VKC; however, the manufacturer considered a worsening (increase) of 1 cm
(10 mm) on any of the four symptoms to warrant initiation of recue therapy.

CFS Responders

A patient was considered a responder if their mean CFS score during the last three months of treatment was 50% or less of the baseline value and if they did not withdraw for a reason related to the treatment, did not experience ulceration, and did not use rescue medication.

Quality of Life in Children with Vernal Keratoconjunctivitis Questionnaire

The Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire is a self-reported questionnaire for measuring health-related quality of life (HRQoL) in children from five years to 12 years of age with allergic conjunctivitis, keratoconjunctivitis, or both.[7] The questionnaire is composed of 16 items in two domains: 12 items in the symptoms domain and four items in the daily activities domain.[7] Each item is rated on a 3-point Likert scale (1 = never, 2 = sometimes, and 3 = always) according to how often the patients experienced symptoms or difficulties with activities in the preceding two weeks.[7] A higher score on an item or in a domain corresponds with worse HRQoL. The raw scores are linearly transformed to a scale ranging from 0 to 100.[7]

Convergent validity of the QUICK symptom domain score was demonstrated through weak to strong correlations with five of six clinical sign scores and total clinical sign score. It was also demonstrated through strong correlations with physical well-being and disease domain score of the KINDL, a generic HRQoL tool. Convergent validity of the QUICK questionnaire daily activities domain score was shown through a moderate correlation with the KINDL disease domain score. The QUICK questionnaire was originally developed and validated in Italian; evidence for the validity of versions with other languages was not found. The QUICK questionnaire domain scores each demonstrated acceptable internal consistency reliability. No evidence for inter-rater and test-retest reliability was found. Similarly, no evidence for the responsiveness of the QUICK questionnaire domain scores was found.

Statistical Analysis

VEKTIS was a randomized, DB, placebo-controlled, clinical trial. The sample size for VEKTIS was calculated based on a previous phase II study where, at one month, the investigators noted a difference of 1.5 grade on the Oxford scale between the active and placebo groups, with an observed standard deviation of 2. As such, the VEKTIS sample size was based on an assumption of achieving a mean difference of 1.25 grade on the Oxford scale in the average of the four assessments. A sample size of 50 patients per

group was required to have 80% power; a two-sided alpha risk of 2.5% was needed to consider multiplicity adjustment for the two tested dose regimens. A provision of 12% was arbitrarily added to the sample size (56 patients per group) for the decrease of power linked to an early end of the VKC season in some regions and possibly early withdrawals.

The approach to dealing with missing data or drop-outs was based on the scenario in which the missing data occurred:

- For missing data related to lack of efficacy, the worst observation (month or baseline) was carried forward.
- For missing data related to lack of safety or lack of tolerance, but not lack of efficacy, the last observation was carried forward.
- For missing data related to symptom relief and or end of season, the best observation (month) was carried forward.
- For missing data independent of treatment, the average of available post-treatment observations was imputed.
- For missing data related to patients lost to follow-up, where there was a complete absence of data, the baseline CFS was carried forward; therefore, the change was equal to zero.
- If data related to an intermediary visit were missing, then the mean of the preceding and following visits was imputed.

The primary analysis of the primary efficacy outcome (mean of the four composite efficacy outcome at each month of the four-month randomized period) was conducted using analysis of covariance with treatment as covariate as well as the baseline CFS and the proportion of time potentially spent taking study medication during the VKC season (i.e., exposure to VKC season). Adjustment for type I error was done through the Hochberg procedure for comparing each dose versus placebo. The procedure started with the largest *P* value compared with 0.05 followed by the smallest *P* value compared with 0.025 if the largest *P* value was not significant. Sensitivity analyses for the primary outcome included: using the per-protocol set, the full analysis set (FAS) with no imputations, and exclusion of the exposure to VKC season from the set of covariates. The primary outcome was further analyzed based on its individual components, with each component's least squares mean difference between the active arm and placebo calculated individually and added together to result in the same result of the overall effect as reported in the primary analysis. Each component's contribution to the overall effect was then outlined as a percentage, where a negative percentage favoured the placebo arm. No subgroup analysis was planned a priori for the primary outcome.

Secondary continuous outcomes (VAS, QUICK questionnaire) were assessed using a general mixed model for repeated measures with baseline as covariate. Responder analysis was conducted through logistic regression using the treatment and the proportion of time spent under treatment during the VKC season as covariates. Frequency distribution of rescue medication for each group was compared with placebo through a non-parametric Savage test. No adjustments for multiple outcomes were conducted for secondary outcomes.

Analysis Populations

The following analysis populations were defined:

- The safety set consisted of all patients randomized in the study for whom there was any evidence that they used study medication and for whom any follow-up information was available.
- The FAS consisted of randomized patients who took at least one dose of study medication. The FAS was used for the primary analysis.
- The per-protocol set excluded FAS patients with any major protocol deviations that may have affected the efficacy analysis.

Results

Patient Disposition

Table 6 summarizes the disposition of enrolled patients. The proportion of patients who discontinued VEKTIS was not balanced across groups. Patients in the twice-daily treatment regimen group had the highest proportion of discontinuations, at 20%. No discontinuations were attributed to AEs; almost half were attributed to lack of efficacy. Patients in the four-times-daily treatment regimen group had the lowest proportion of discontinuation, at 10%. For the placebo group, the figure was 15.8%.

Table 6: Patient Disposition – Four-Month Randomized Period

Title	VEKTIS		
	0.1% Cyclosporine 4 Times Daily	0.1% Cyclosporine 2 Times Daily	Vehicle (Placebo)
Screened, N	Not reported	Not reported	Not reported
Randomized, N	57	55	57
Discontinued/withdrew from study, N (%)	6 (10.5)	11 (20.4)	9 (15.5)
Reason for discontinuation, N (%)			
Adverse events	2	0	2
Lost to follow-up	0	1	0
Lack of efficacy	1	5	5
Decision unrelated to adverse events	2	3	2
Investigator decision	1	1	0
Other	0	1	0
FAS, N	56	54[a]	58[b]
PP, N	52	52	55
Safety, N	57[c]	54	58

FAS = full analysis set; PP = per-protocol; VEKTIS = Vernal KeratoconjunctiviTIs Study.

[a] One patient was excluded from the FAS in the twice-daily arm due to violation of the main inclusion criteria

[b] For one patient, the planned treatment was four times daily, but the initial treatment actually received was placebo due to incorrect allocation; thus, this patient was counted in the placebo arm in the FAS.

[c] One patient allocated to the twice-daily arm received four-times-daily treatment on several occasions. This patient is considered part of the four-times-daily safety set arm.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Exposure to study treatments

Table 7 summarizes treatment exposure. The majority of patients across the study's groups achieved a treatment exposure greater than 84 days and an adherence greater than 90%.

Table 7: Summary of Extent of Exposure in the Four-Month Randomized Period (Safety Set)

	VEKTIS		
	0.1% Cyclosporine 4 Times Daily N = 57	0.1% Cyclosporine 2 Times Daily N = 54	Vehicle (Placebo) N = 58
Exposure (days), n (%)			
< 28	[redacted]	[redacted]	[redacted]
28 to 56	[redacted]	[redacted]	[redacted]
56 to 84	[redacted]	[redacted]	[redacted]
84 to 112	[redacted]	[redacted]	[redacted]
112 >	[redacted]	[redacted]	[redacted]
Adherence, n (%)			
< 80	[redacted]	[redacted]	[redacted]
80 to 90	[redacted]	[redacted]	[redacted]
90 to 100	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]

VEKTIS = Vernal KeratoconjunctiviTIs Study.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Efficacy – Four-Month Randomized Period

Only the efficacy outcomes and subgroup analyses identified in the review protocol are reported.

VEKTIS Primary Efficacy Result – Penalties-Adjusted Composite Efficacy Score

The primary outcome in VEKTIS showed that both regimens of cyclosporine 0.1% were statistically significantly better than placebo, with a between-group difference of 0.76 in the least squares mean for the four-times-daily treatment regimen group versus the placebo group (95% confidence interval [CI], 0.26 to 1.27, $P = 0.007$) and a between-group difference of 0.67 in the least squares mean for the twice-daily treatment regimen group versus the placebo group (95% CI, 0.16 to 1.18, $P = 0.01$). The sensitivity analyses using the per-protocol set, the FAS with no imputations, and the exclusion of exposure to the VKC season from the set of covariates all showed results that were similar to the base-case analysis. Table 8 provides an overview of the efficacy composite scores at each month and the overall average.

Table 8: Penalties-Adjusted Composite Efficacy Score at Each Visit and Primary End Point (FAS)

	Total N	Baseline Score	End-of-Treatment Time Point		Treatment Group Difference Versus Control		
		Mean (SD)	Mean (SD)	Mean Change From Baseline (SE)	N	Least Squares Mean Difference (95% CI)	*P* Value[b]
Primary End Point (Average Penalties-Adjusted CFS Score Over the 4 Months) [a]							
0.1% cyclosporine 4 times daily	56	NA	2.06 (1.44)	NA	56	0.76 (0.26 to 1.27)	**0.007**
0.1% cyclosporine 2 times daily	54	NA	1.93 (1.37)	NA	54	0.67 (0.16 to 1.18)	**0.010**
Vehicle	58	NA	1.34 (1.22)	NA	58	Ref	Ref
Month 1							
0.1% cyclosporine 4 times daily	56	NA	1.51 (1.51)	NA	NA	NA	NA
0.1% cyclosporine 2 times daily	54	NA	1.19 (1.46)	NA	NA	NA	NA
Vehicle	58	NA	0.72 (1.41)	NA	NA	NA	NA
Month 2							
0.1% cyclosporine 4 times daily	56	NA	1.81 (1.64)	NA	NA	NA	NA
0.1% cyclosporine 2 times daily	54	NA	2.06 (1.56)	NA	NA	NA	NA
Vehicle	58	NA	1.09 (1.4)	NA	NA	NA	NA
Month 3							
0.1% cyclosporine 4 times daily	56	NA	2.42 (1.79)	NA	NA	NA	NA
0.1% cyclosporine 2 times daily	54	NA	2.28 (1.61)	NA	NA	NA	NA
Vehicle	58	NA	1.69 (1.62)	NA	NA	NA	NA
Month 4							
0.1% cyclosporine 4 times daily	56	NA	2.51 (1.79)	NA	NA	NA	NA
0.1% cyclosporine 2 times daily	54	NA	2.19 (1.65)	NA	NA	NA	NA
Vehicle	58	NA	1.87 (1.59)	NA	NA	NA	NA

CFS = corneal fluorescein staining; CI = confidence interval; FAS = full analysis set; NA = not applicable; Ref = reference; SD = standard deviation; SE = standard error.

[a] The primary end point analysis was conducted using analysis of covariance with treatment as covariate as well as the baseline CFS and the proportion of time potentially spent taking study medication during the VKC season.

[b] Adjustment for type I error was done through the Hochberg's procedure for comparing each dose versus placebo.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

The contribution of each component of the composite efficacy score is summarized in Table 9. The analysis shows that 70.3% of improvements observed in the four-times-daily treatment regimen group, and 77.6% of improvements observed in the twice-daily treatment regimen group, were driven by improvements in the CFS score. The mean number of ulcer occurrences contributed minimally to the composite efficacy score.

Table 9: Contribution of the Three Components of the Primary End Point (Full Analysis Set)

Title	VEKTIS		
	0.1% Cyclosporine 4 Times Daily	0.1% Cyclosporine 2 Times Daily	Vehicle (Placebo)
Mean change from baseline of the mean CFS score per month			
LS mean (absolute contribution)	0.523	0.528	Ref
95% CI	(0.109 to 0.937)	(0.113 to 0.943)	Ref
Adjusted *P* value*	0.014	0.014	Ref
Relative contribution (%)	70.3%	77.6%	Ref
Mean number of rescue medication courses per month			
LS mean (absolute contribution)	0.220	0.149	Ref
95% CI	(0.068 to 0.372)	(–0.003 to 0.301)	Ref
Adjusted *P* value*	0.010	0.055	Ref
Relative contribution (%)	29.6%	21.9%	Ref
Mean number of ulcer occurrences per month			
LS mean (absolute contribution)	0.001	0.003	Ref
95% a	(–0.036 to 0.038)	(–0.033 to 0.040)	Ref
Adjusted *P* value[a]	0.966	0.966	Ref
Relative contribution (%)	0.1%	0.5%	Ref

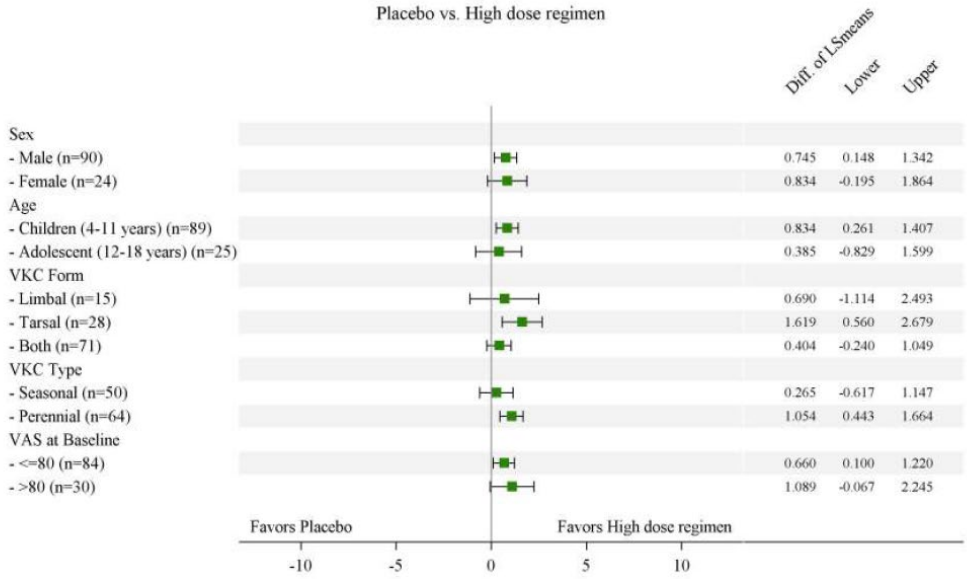
CFS: corneal fluorescein staining; CI = confidence interval; LS = least squares; Ref = reference; VEKTIS = Vernal KeratoconjunctiviTIs Study.

[a] Hochberg procedure.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Results of unplanned subgroups analyses of the primary outcomes are displayed as forest plots in Figure 2 and Figure 3.

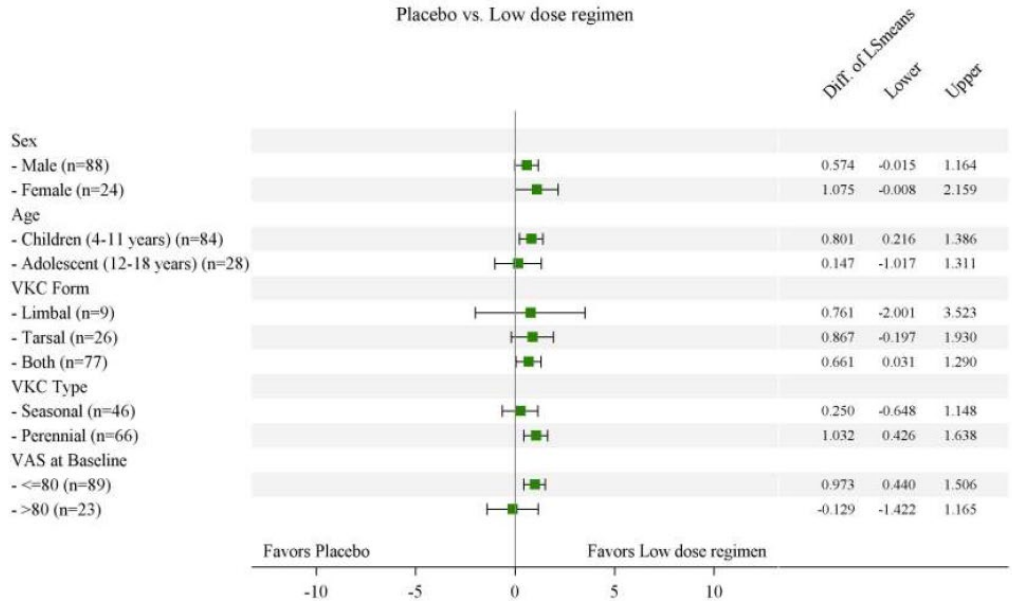
Figure 2: Subgroups Forest Plot of Four-Times-Daily Cyclosporine 0.1% Versus Placebo Comparison in Primary End Point (FAS)



Diff. = difference; FAS = full analysis set; LS = least squares; VAS: visual analogue scale; VKC = vernal keratoconjunctivitis; vs. = versus.

Source: CADTH Common Drug Review submission: Verkazia (cyclosporine), topical ophthalmic emulsion, 0.1% w/v [**CONFIDENTIAL** manufacturer's submission].[8,15]

Figure 3: Subgroups Forest Plot of Twice-Daily Cyclosporine 0.1% Versus Placebo Comparison in Primary End Point (FAS)



Diff. = difference; FAS = full analysis set; LS = least squares; VAS: visual analogue scale; VKC = vernal keratoconjunctivitis; vs. = versus.

Source: CADTH Common Drug Review submission: Verkazia (cyclosporine), topical ophthalmic emulsion, 0.1% w/v [**CONFIDENTIAL** manufacturer's submission].[8]

Visual Analogue Scale for Photophobia, Tearing, Itching, and Mucous Discharge

A summary of the outcome is presented in Table 10. The average of the measurements of the four symptoms indicated larger improvements in the four-times-daily treatment regimen group versus placebo (least squares mean difference: –19.411 [95% CI, –29.307 to –9.515]) than in the twice-daily treatment regimen group versus placebo (least squares mean difference: –8.355 [95% CI, –18.402 to 1.693]). It is also apparent that the 95% CI in the twice-daily treatment regimen group spans the null.

Table 10: Results for Visual Analogue Scale for Photophobia, Tearing, Itching, and Mucous Discharge (FAS)

	Total N	Baseline Score	End-of-Treatment Time Point (Month 4)	Treatment Group Difference Versus Control		
		Mean (SD)	Mean (SD)	N	Least Squares Mean Difference (95% CI)	*P* Value[b]
VAS – mm[a]						
Photophobia						
0.1% cyclosporine 4 times daily	56	78.5 (17.6)	29.1 (34.9)	56	–20.861 (–32.364 to –9.357)	< 0.001
0.1% cyclosporine 2 times daily	54	69.9 (24.2)	38.9 (36.0)	54	–6.715 (–18.487 to 5.056)	0.262
Vehicle	58	76.5 (15.8)	48.8 (32.8)	58	Ref	
Tearing						
0.1% cyclosporine 4 times daily	56	72 (19.6)	24.4 (31.3)	56	–15.606 (–26.248 to –4.964)	0.009
0.1% cyclosporine 2 times daily	54	72.6 (14.2)	32.8 (33.5)	54	–8.999 (–19.840 to 1.842)	0.103
Vehicle	58	65.4 (21.7)	38.5 (28.5)	58	Ref	
Itching						
0.1% cyclosporine 4 times daily	56	78.0 (18.2)	27.0 (34.0)	56	–19.455 (–30.581 to –8.328)	0.001
0.1% cyclosporine 2 times daily	54	80.1 (14.8)	38.0 (36.5)	54	–10.883 (–22.232 to 0.466)	0.060
Vehicle	58	78.4 (16.3)	46.5 (31.5)	58	Ref	
Mucous Discharge						
0.1% cyclosporine 4 times daily	56	74.2 (22.1)	24.6 (32.0)	56	–17.955 (–29.568 to –6.343)	0.005
0.1% cyclosporine 2 times daily	54	67.7 (21.6)	34.2 (35.9)	54	–6.933 (–18.767 to 4.900)	0.249
Vehicle	58	70.4 (17.8)	41.0 (33.8)	58	Ref	

	Total N	Baseline Score	End-of-Treatment Time Point (Month 4)	Treatment Group Difference Versus Control		
		Mean (SD)	Mean (SD)	N	Least Squares Mean Difference (95% CI)	*P* Value[b]
Average of the 4 Measurements						
0.1% cyclosporine 4 times daily	56	75.7 (11.2)	26.0 (29.8)	56	–19.411 (–29.307 to –9.515)	< 0.001
0.1% cyclosporine 2 times daily	54	72.6 (9.3)	36.0 (32.4)	54	–8.355 (–18.402 to 1.693)	0.103
Vehicle	58	72.7 (9.5)	43.4 (27.3)	58	Ref	

CI = confidence interval; FAS = full analysis set; Ref = reference; SD = standard deviation; VAS = visual analogue scale.
[a] The end point analysis was conducted using a general mixed model for repeated measures, with baseline as covariate.
[b] Outcome not adjusted for multiplicity.
Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

CFS Responder

The proportions of responders in the four-times-daily treatment regimen group and twice-daily treatment regimen group were 57.1% and 61.1%, respectively, versus the placebo group, where 34.5% of patients met the responder definition. Responders were defined as those who had a mean CFS score during the last three months of treatment that was 50% or less of the baseline value, and who did not withdraw for a reason related to treatment, did not experience ulceration, and did not use rescue medication. Table 11 summarizes the outcome.

Table 11: Corneal Fluorescein Staining Score Responders (Full Analysis Set)

Title	VEKTIS		
	0.1% Cyclosporine 4 Times Daily	0.1% Cyclosporine 2 Times Daily	Vehicle (Placebo)
Month 4 responders[a]			
n	56	54	58
Responder rate	32 (57.1%)	33 (61.1%)	20 (34.5%)
Odds ratio (vs. placebo)	2.583	3.486	Ref
95% CI	(1.207 to 5.531)	(1.576 to 7.713)	Ref
P value[b]	0.015	0.004	Ref

CI = confidence interval; Ref = reference; VEKTIS = Vernal KeratoconjunctiviTIs Study; vs. = versus.
[a] The end point analysis was conducted using a logistic regression, with the treatment and proportion of time spent under treatment during the VKC season as covariates.
[b] Outcome not adjusted for multiplicity.
Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Rescue Medication

Table 12 provides a summary of rescue medication given to patients in the four-month randomized DB phase. Patients in the cyclosporine 0.1% four-times-daily treatment regimen group received at least one rescue medication at a rate of 0.321 (95% CI, 0.203 to 0.460), and patients in the twice-daily treatment regimen group received it at a rate of 0.315 (95% CI, 0.195 to 0.456), compared with the placebo group, where patients received at least one rescue medication at a rate of 0.534 (95% CI, 0.399 to 0.667).

Table 12: Summary of Number of Courses of Rescue Medication (Full Analysis Set)

Number of Rescue Medications	VEKTIS		
	0.1% Cyclosporine 4 Times Daily	0.1% Cyclosporine 2 Times Daily	Vehicle (Placebo)
Proportion of patients with at least 1 use of rescue medication over the study treatment period			
Rate	0.321	0.315	0.534
95% CI	(0.203 to 0.460)	(0.195 to 0.456)	(0.399 to 0.667)
Month 1			
n	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Month 2			
n	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Month 3			
n	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Month 4			
n	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]

CI = confidence interval; VEKTIS = Vernal KeratoconjunctiviTIs Study.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Quality of Life in Children with Vernal Keratoconjunctivitis Questionnaire

Table 13 provides a summary of the results of the QUICK questionnaire's two domains at baseline and at each month. The four-times-daily treatment regimen group consistently achieved a larger magnitude of benefit versus placebo than the twice-daily treatment

regimen group did. However, note that the data are severely skewed to the right in the daily activities domain.

Table 13: Summary of Results of the QUICK Questionnaire (Full Analysis Set)

	Total N	Baseline Score		End-of-Treatment Time Point		Treatment Group Difference Versus Control		
		Mean (SD)	Median (Min, Max)	Mean (SD)	Median (Min, Max)	N	Least Squares Mean Difference (95% CI)	*P* Value[b]
Symptoms Domain[a]								
Month 1								
0.1% cyclosporine 4 times daily	56	61.1 (18.8)	[redacted]	38.8 (21.4)	[redacted]	56	–9.684 (–17.729 to –1.639)	0.037
0.1% cyclosporine 2 times daily	54	59 (17.6)	[redacted]	41.6 (21.9)	[redacted]	54	–6.744 (–14.979 to 1.491)	0.108
Vehicle	58	63.2 (17.6)	[redacted]	49.3 (20.2)	[redacted]	58	Ref	Ref
Month 2								
0.1% cyclosporine 4 times daily	56	61.1 (18.8)	[redacted]	32.9 (22.4)	[redacted]	56	–15.646 (–23.585 to –7.707)	< 0.001
0.1% cyclosporine 2 times daily	54	59 (17.6)	[redacted]	35.8 (21.9)	[redacted]	54	–12.585 (–20.714 to –4.455)	0.003
Vehicle	58	63.2 (17.6)	[redacted]	49.3 (19.7)	[redacted]	58	Ref	Ref
Month 3								
0.1% cyclosporine 4 times daily	56	61.1 (18.8)	[redacted]	28.6 (24.1)	[redacted]	56	–12.075 (–19.812 to –4.337)	0.005
0.1% cyclosporine 2 times daily	54	59 (17.6)	[redacted]	34 (25.1)	[redacted]	54	–15.646 (–23.585 to –7.707)	0.11
Vehicle	58	63.2 (17.6)	[redacted]	41.5 (20.8)	[redacted]	58	Ref	Ref
Month 4								
0.1% cyclosporine 4 times daily	56	61.1 (18.8)	[redacted]	27.6 (23.3)	[redacted]	56	–8.766 (–16.403 to –1.129)	0.049
0.1% cyclosporine 2 times daily	54	59 (17.6)	[redacted]	32.4 (26.2)	[redacted]	54	–3.817 (–11.646 to 4.013)	0.338
Vehicle	58	63.2 (17.6)	[redacted]	37.1 (22.5)	[redacted]	58	Ref	Ref
Daily Activities Domain[a]								
Month 1								
0.1% cyclosporine 4 times daily	56	33.9 (26.7)	[redacted]	15 (22.5)	[redacted]	56	–7.995 (–16.565 to 0.576)	0.135
0.1% cyclosporine 2 times daily	54	31.4 (28.9)	[redacted]	17.4 (22.5)	[redacted]	54	–6.129 (–14.845 to 2.588)	0.167

	Total N	Baseline Score		End-of-Treatment Time Point		Treatment Group Difference Versus Control		
		Mean (SD)	Median (Min, Max)	Mean (SD)	Median (Min, Max)	N	Least Squares Mean Difference (95% CI)	*P* Value[b]
Vehicle	58	29.7 (27.4)	[redacted]	22 (25)	[redacted]	58		
Month 2								
0.1% cyclosporine 4 times daily	56	33.9 (26.7)	[redacted]	13 (21.8)	[redacted]	56	–9.321 (–18.525 to –0.117)	0.047
0.1% cyclosporine 2 times daily	54	31.4 (28.9)	[redacted]	12.7 (22.1)	[redacted]	54	–10.076 (–19.427to –0.725)	0.047
Vehicle	58	29.7 (27.4)	[redacted]	21.3 (30.1)	[redacted]	58		
Month 3								
0.1% cyclosporine 4 times daily	56	33.9 (26.7)	[redacted]	8.3 (16)	[redacted]	56	–11.425 (–19.569 to –3.281)	0.012
0.1% cyclosporine 2 times daily	54	31.4 (28.9)	[redacted]	13.2 (24.6)	[redacted]	54	–6.917 (–15.207 to 1.373)	0.101
Vehicle	58	29.7 (27.4)	[redacted]	18.7 (28.1)	[redacted]	58		
Month 4								
0.1% cyclosporine 4 times daily	57	33.9 (26.7)	[redacted]	5.7 (13.4)	[redacted]	56	–10.33 (–17.462 to –3.198)	0.009
0.1% cyclosporine 2 times daily	54	31.4 (28.9)	[redacted]	11.4 (22.8)	[redacted]	54	–5.07 (–12.348 to 2.208)	0.171
Vehicle	58	29.7 (27.4)	[redacted]	15 (25.3)	[redacted]	58		

CI = confidence interval; Ref = reference; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SD = standard deviation.

[a] The end point analysis was conducted using a general linear mixed model for repeated measures. The baseline was used as covariate.

[b] Outcome not adjusted for multiplicity.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Harms – Four-Month Randomized Period

Only those harms identified in the review protocol are reported. See Table 14 for detailed harms data.

Adverse Events

Patients in the twice-daily treatment regimen group had the lowest proportion of the number of patients with at least one AE (33.3%). In contrast, the placebo group had a proportion of 39.7% and the four-times-daily treatment regimen group had a proportion of 42.1%. "Instillation site pain" was reported by six patients (10.5%) in the four-times-daily treatment regimen group, three patients (5.6%) in the twice-daily treatment regimen group, and two patients (3.4%) in the placebo group.

Serious Adverse Events

Three serious adverse events (SAEs) were reported in the study: two in the four-times-daily regimen group (tibial fracture and phimosis) and one in the twice-daily regimen group (head injury).

Withdrawal Due to Adverse Events

During the four-month, DB efficacy phase, the placebo group had the highest number of withdrawal due to adverse events (WDAEs), with four patients (6.9%) withdrawing. The four-times-daily treatment regimen group had three WDAEs (5.3%). There were no WDAEs in the twice-daily treatment regimen group.

Mortality

No deaths were reported in VEKTIS.

Notable Harms

While stinging sensation was not explicitly reported, the manufacturer reported that during the DB phase, "instillation site pain" was reported by six patients (10.5%) in the four-times-daily treatment regimen group, by three patients (5.6%) in the twice-daily treatment regimen group, and by two patients (3.4%) in the placebo group. Eye infections were reported in the form of ulcerative keratitis (7.0%, 5.6%, and 5.2% in the four-times-daily, twice-daily, and placebo groups, respectively).

Table 14: Summary of Harms – Four-Month Randomization Period

	VEKTIS		
	0.1% Cyclosporine 4 Times Daily N = 57	0.1% Cyclosporine 2 Times Daily N = 54	Vehicle (Placebo) N = 58
Patients with ≥ 1 adverse event			
n (%)	24 (42.1%)	18 (33.3%)	23 (39.7%)
Most common events[a]			
EYE DISORDERS	[redacted]	[redacted]	[redacted]
Ulcerative keratitis	4 (7.0%)	3 (5.6%)	3 (5.2%)
Corneal leukoma	2 (3.5%)	0	1 (1.7%)
Eye irritation	1 (1.8%)	0	1 (1.7%)

	VEKTIS		
	0.1% Cyclosporine 4 Times Daily N = 57	0.1% Cyclosporine 2 Times Daily N = 54	Vehicle (Placebo) N = 58
Eye pain	1 (1.8%)	1 (1.9%)	0
Foreign body sensation in eyes	2 (3.5%)	0	0
Ocular hyperemia	1 (1.8%)	0	1 (1.7%)
Blepharospasm	1 (1.8%)	0	0
Cataract, subcapsular	0	0	1 (1.7%)
Chalazion	1 (1.8%)	0	0
Conjunctivitis	0	0	1 (1.7%)
Corneal deposits	0	0	1 (1.7%)
Erythema of eyelid	1 (1.8%)	0	0
Eyelid erosion	1 (1.8%)	0	0
Eyelid oedema	0	0	1 (1.7%)
Visual acuity reduced	0	0	1 (1.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	[redacted]	[redacted]
Instillation site pain	[redacted]	[redacted]	[redacted]
Instillation site pruritus	[redacted]	[redacted]	[redacted]
Instillation site erythema	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Application site discharge	[redacted]	[redacted]	[redacted]
Application site swelling	[redacted]	[redacted]	[redacted]
Instillation site irritation	[redacted]	[redacted]	[redacted]
INFECTIONS AND INFESTATIONS	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Hordeolum	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Bronchiolitis	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Gastroenteritis, viral	[redacted]	[redacted]	[redacted]
Otitis externa	[redacted]	[redacted]	[redacted]
Parasitic gastroenteritis	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Asthma	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Allergic respiratory disease	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]

	VEKTIS		
	0.1% Cyclosporine 4 Times Daily N = 57	0.1% Cyclosporine 2 Times Daily N = 54	Vehicle (Placebo) N = 58
Sneezing	[redacted]	[redacted]	[redacted]
Throat tightness	[redacted]	[redacted]	[redacted]
NERVOUS SYSTEM DISORDERS	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]
Dermatitis, allergic	[redacted]	[redacted]	[redacted]
Papule	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 serious adverse event			
n (%)	2 (3.5)	1 (1.9)	0 (0)
Most common events			
Head injury	0	1	0
Tibia fracture	1	0	0
Ulcerative keratitis	1	0	0
Patients who stopped treatment due to adverse events			
n (%)	3 (5.3)	0	4 (6.9)
Most common events[a]			
	Not reported	Not reported	Not reported
Deaths			
n (%)	0	0	0
Notable harms			
Ulcerative keratitis	4 (7.0%)	3 (5.6%)	3 (5.2%)
Conjunctivitis	0	0	1 (1.7%)
Stinging, n (%)	0	0	0

VEKTIS = Vernal KeratoconjunctiviTIs Study.

[a] Frequency > 5%.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Critical Appraisal

Internal Validity

VEKTIS was a randomized, sham procedure–controlled, DB clinical trial. The study methods were generally well reported (as summarized previously), including the details of randomization, allocation concealment, and statistical analysis. Overall, potential issues pertaining to the internal validity of the study can be identified as relating to the following points:

1) Noticeable imbalances in baseline characteristics:

Patients randomized to the four-times-daily cyclosporine 0.1% treatment regimen group showed a tendency to be diagnosed with a more severe form of VKC than patients in the other two arms; there was a clear imbalance in the CFS score at baseline, where 25.0% of patients in the four-times-daily treatment arm were diagnosed as grade 4. This contrasts with 9.3% in the twice-daily group and 6.9% in the placebo group. A similar imbalance was observed regarding the Bonini scale, but to a lesser extent: 42.9% of patients in the four-times-daily regimen, 40.7% of patients in the twice-daily regimen, and 31.0% of patients in the placebo group were assessed as grade 4 on that scale. Although the baseline CFS score was adjusted for in the primary analysis of the primary efficacy outcome, the fact that CFS score is the primary driver in the efficacy model makes it unclear how to interpret the extent of the effect of the imbalance potentially controlled for. At the request of Health Canada, the manufacturer conducted a post hoc sensitivity analysis where patients where stratified by severity. The results did not lead to a conclusive confounding effect for potential imbalances in baseline severity.[14]

2) Use of outcomes with no established validity in the patient population:

The primary outcome of VEKTIS was an average of four composite efficacy outcomes based on changes in the modified Oxford scale adjusted by penalties for the use of rescue medication or the occurrence of corneal ulcerations. The rationale provided for using this scale was that it considers signs (keratitis, as assessed by CFS), symptoms (as rescue therapy would be used for worsening symptoms), and the use of corticosteroids, which are associated with harms in VKC patients.[8] However, the manufacturer did not provide a sensitivity analysis of the different effects that various penalty scores may have had on the outcome. Also, the modified Oxford scale was developed to detect keratitis in dry eye disease; the validity of the tool is undetermined in the VKC patient population. In its advice to the manufacturer, CHMP considered each part of the composite end point to be clinically meaningful and potentially sensitive in detecting an overall treatment effect.[8] However, a validation study along with an understanding of the reliability and responsiveness of such outcomes does not exist — a fact that may raise concerns about the robustness of the finding. In addition, the analysis of the composite primary end point assumes normality in the distribution in a linear model. Considering the use of the modified Oxford scale (which can assign only values of 0, 0.5, 1, 2, 3, 4, and 5), the baseline values (where patients were mostly in the severe range), and the integer nature of the penalties, the averaging of the four observations is unlikely to provide sufficient variability and continuity in the data to justify a normality assumption.

In addition to the primary composite efficacy score, the manufacturer used a 100 mm VAS to measure patients' symptoms. There is no evidence of the validity, reliability, or responsiveness of such a tool for patients with VKC. In addition, considering the use of patient-reported outcomes in pediatric patients, parental involvement is highly likely, which

may add another layer of subjectivity and increase the variability of the patient-reported outcome measures. It is not clear which direction of potential bias these points might have led to.

3) Imbalance in the proportion of patients who discontinued and the lack of comprehensive sensitivity analysis to assess the impact of data imputations:

Across the three study arms, patients discontinued the study at different proportions. The highest discontinuation rate was in the twice-daily arm (20%), followed by the placebo arm (15.8%); the rate was lowest in the four-times-daily arm (10.5%). The manufacturer proposed a data imputation method based on the specific context in which missing data occurred. For data missing due to lack of efficacy, the missing data were imputed with the worst observation. About half of the patients who discontinued in the twice-daily and placebo arms (five out of 11 and five out of nine, respectively) did so due to lack of efficacy, while only one patient out of six in the four-times-daily treatment arm did so. It is likely that the differential discontinuation rate compounded with the differential worst observation carried forward imputation biased the result in favour of the four-times-daily arm. The manufacturer ran a sensitivity analysis using observed data only. This analysis showed similar results to the base case. However, analysis using observed data only is not sufficient to estimate the effect of the data imputation method. Both the primary imputation method and the sensitivity analysis are likely to be biased in favour of the four-times-daily treatment regimen. Further sensitivity analyses are required to investigate the extent of the bias.

4) Conducting unplanned subgroup analyses:

The manufacturer provided subgroup analyses for patients based on various baseline characteristics. These subgroups were not planned a priori. In addition, considering the small sample size, many of these subgroups may not have had a sufficient number of patients to produce robust results.

5) Lack of control for multiplicity in outcomes beyond the primary outcome:

Considering the composite nature of the primary outcome, identifying clinically relevant secondary outcomes with adjustment for multiple testing would have been helpful in interpreting the study's results. However, secondary outcomes (e.g., QUICK scores) were not adjusted for multiplicity.

External Validity

VEKTIS is a multi-centre study that included sites in the US, Europe, and India. It did not include any sites in Canada. However, according to the clinical experts, the study's inclusion and exclusion criteria and baseline demographics data reflect the patient population commonly seen in Canadian settings and diagnosed with severe VKC. The clinical experts have communicated that if they applied the inclusion and exclusion criteria to their patients with severe VKC, the vast majority would be eligible for enrolment. The clinical experts also reported that compounded cyclosporine is already commonly used in cases where symptoms and signs are severe enough to otherwise require high-dose or extended treatment with corticosteroids, and that VEKTIS captured this patient population. Also, the duration of VEKTIS was appropriate in capturing the VKC season, and the eight-month follow-up period was helpful in terms of understanding potential safety or long-term efficacy issues.

An important limitation to the external validity of VEKTIS is the difficulty in the clinical interpretation of the primary outcome as well as the clinical interpretation of the secondary outcomes that are not adjusted for multiplicity. In the absence of established validity and an MCID in the primary outcome, clinical interpretation of the magnitude of the observed difference between the active treatment groups and placebo group is not possible. The clinical experts consulted in this review recognize that each component of the primary outcome is clinically relevant. However, the composite efficacy outcome is not a measure that would be used in clinical practice. Also, with the placebo-based comparison, we are not able to extrapolate the results of the treatment difference versus placebo to the comparators of interest identified in the CDR review protocol. VEKTIS provided clinically relevant outcomes in the form of secondary outcomes. However, these are not adjusted for multiplicity; as such, it is not possible to use statistical inference to apply the results from the study sample to the Canadian patient population.

A concern regarding the generalizability of the results of VEKTIS is the expected low adherence in clinical practice as opposed to the more controlled environment (leading to higher adherence) in study settings. The clinical experts consulted in this review reported that adherence to treatment is a challenge in some VKC patients. While patients in VEKTIS showed high levels of adherence to the study's assigned treatment, this is known to be a challenge in clinical practice. Thus, adherence in VEKTIS may not reflect clinical practice. This may limit the generalizability of the observed improvements reported in VEKTIS.

Indirect Evidence

No indirect evidence was submitted by the manufacturer or identified in our literature search that would match the inclusion and exclusion criteria of this review.

Other Relevant Evidence

VEKTIS included an eight-month safety follow-up phase. This phase also reported some exploratory efficacy outcomes. It is summarized in this section.

VEKTIS Eight-Month Follow-up Period

Overview

At the discretion of the investigator, patients who successfully completed the initial four-month phase of the study were allowed to continue on the medication regimen they had been assigned to for another eight months. Patients who had been randomized to the placebo group were randomized in an equal manner to the four-times-daily and twice-daily cyclosporine 0.1% groups. As a result, three subgroups of patients developed:

- subgroup A: patients who stopped the treatment at month 4 and did not use it again until month 12
- subgroup B: patients who did not stop their treatment at month 4 and continued it in a chronic manner
- subgroup C: patients who used the active treatment intermittently as needed.

A summary of the subgroups of patients by exposure and treatment intake is available in Table 15. A total of 142 patients were enrolled in period 2 of VEKTIS, presenting 84.0% of the total number of patients randomized at the beginning of the study.

Table 15: Subgroups in Period 2 by Treatment Assignment and Exposure

	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 50)	Vehicle (Placebo) (N = 22)	Total (N = 72)	Twice-Daily Regimen (N = 44)	Vehicle (Placebo) (N = 26)	Total (N = 70)
Subgroup A	1 (2.0)	3 (13.6)	4 (5.6)	4 (9.1)	1 (3.8)	5 (7.1)
N (%)						
Subgroup B						
N (%)	29 (58.0)	13 (59.1)	42 (58.3)	25 (56.8)	17 (65.4)	42 (60.0)
Mean number of days	[redacted]	[redacted]	231.5	[redacted]	[redacted]	215.4
Subgroup C						
N (%)	20 (40.0)	6 (27.3)	26 (36.1)	15 (34.1)	8 (30.8)	23 (32.9)
Average duration (days) of cyclosporine 0.1%	[redacted]	[redacted]	132.3	[redacted]	[redacted]	126.4

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

The analysis was presented as summary statistics and mean difference from baseline; baseline was considered to be four months. No formal analysis methods or adjustments were conducted. The analysis used a follow-up total set that consisted of all patients who entered the eight-month safety follow-up period. As only a small number of patients ended up in subgroup A, the analysis provided by the manufacturer focused on subgroups B and C only.

Efficacy

Corneal Fluorescein Staining Score

Table 16 and Table 17 provide summaries of changes in CFS scores at each assessment point in VEKTIS period 2 in subgroup B (chronic use) and subgroup C (intermittent use). A negative value indicates an improvement in the CFS score. Overall, in subgroup B, consistent but stable improvement was observed in all patients. It can be noticed that, numerically, improvements in CFS scores were higher in patients who switched from the placebo group. In subgroup C, all patients showed fluctuations between improving and worsening CFS scores from one assessment visit to another except for those who had switched from the placebo group to the four-times-daily group; these patients experienced small but stable improvements in their CFS scores across assessment visits.

Table 16: CFS Change From Baseline (Month 4) in Subgroup B at Each Visit in the Eight-Month Follow-Up Period (FU-TS)

	Subgroup B					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 29)	Vehicle (Placebo) (N = 13)	Total (N = 42)	Twice-Daily Regimen (N = 25)	Vehicle (Placebo) (N = 17)	Total (N = 42)
Month 6						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	–0.50	[redacted]	[redacted]	–0.54
SD	[redacted]	[redacted]	0.91	[redacted]	[redacted]	1.23
Month 8						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12/early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	–1.27	[redacted]	[redacted]	–0.93	[redacted]
SD	[redacted]	1.36	[redacted]	[redacted]	1.71	[redacted]

CFS = corneal fluorescein staining; FU-TS = follow-up total set; SD = standard deviation.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Table 17: CFS Change From Baseline (Month 4) in Subgroup C at Each Visit in the Eight-Month Follow-Up Period (FU-TS)

	Subgroup C					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 20)	Vehicle (Placebo) (N = 6)	Total (N = 26)	Twice-Daily Regimen (N = 15)	Vehicle (Placebo) (N = 8)	Total (N = 23)
Month 6						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	–0.33	[redacted]	[redacted]	–0.22
SD	[redacted]	[redacted]	1.02	[redacted]	[redacted]	0.91
Month 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Subgroup C					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 20)	Vehicle (Placebo) (N = 6)	Total (N = 26)	Twice-Daily Regimen (N = 15)	Vehicle (Placebo) (N = 8)	Total (N = 23)
SD	[redacted]					
Month 12/early termination	[redacted]					
n	[redacted]					
Mean	[redacted]					
SD	[redacted]					

CFS = corneal fluorescein staining; FU-TS = follow-up total set; SD = standard deviation.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Visual Analogue Scale

Table 18 and Table 19 provide a summary of changes in the average four VAS scores at each assessment point in VEKTIS period 2 in subgroup B (chronic use) and subgroup C (intermittent use). A negative value indicates improvement.

[redacted]

Table 18: VAS Average of Four Symptoms – Change From Baseline (Month 4) in Subgroup B at Each Visit in the Eight-Month Follow-Up Period (FU-TS)

	Subgroup B					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 29)	Vehicle (Placebo) (N = 13)	Total (N = 42)	Twice-Daily Regimen (N = 25)	Vehicle (Placebo) (N = 17)	Total (N = 42)
Month 6	[redacted]					
n	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Month 8	[redacted]					
n	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Month 10	[redacted]					
n	[redacted]					
Mean	[redacted]					
SD	[redacted]					

	Subgroup B					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 29)	Vehicle (Placebo) (N = 13)	Total (N = 42)	Twice-Daily Regimen (N = 25)	Vehicle (Placebo) (N = 17)	Total (N = 42)
Month 12/early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FU-TS = follow-up total set; SD = standard deviation; VAS – visual analogue scale.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Table 19: VAS Average of Four Symptoms – Change From Baseline (Month 4) in Subgroup C at Each Visit in the Eight-Month Follow-Up Period (FU-TS)

	Subgroup C					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 20)	Vehicle (Placebo) (N = 6)	Total (N = 26)	Twice-Daily Regimen (N = 15)	Vehicle (Placebo) (N = 8)	Total (N = 23)
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12/early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FU-TS = follow-up total set; SD = standard deviation; VAS – visual analogue scale.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Rescue Medication

Overall, the number of patients receiving rescue medication was stable, with the exception of an increase at the end of the follow-up period in subgroup C patients.

Table 20: Number of Courses of Rescue Medication in Subgroup B (FU-TS)

	Subgroup B					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 29)	Vehicle (Placebo) (N = 13)	Total (N = 42)	Twice-Daily Regimen (N = 25)	Vehicle (Placebo) (N = 17)	Total (N = 42)
Month 4 to month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 to month 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 8 to month 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 10 to month 12/early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FU-TS = follow-up total set.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Table 21: Number of Courses of Rescue Medication in Subgroup C (FU-TS)

	Subgroup C					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 29)	Vehicle (Placebo) (N = 13)	Total (N = 42)	Twice-Daily Regimen (N = 25)	Vehicle (Placebo) (N = 17)	Total (N = 42)
Month 4 to month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 to month 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 8 to month 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 10 to month 12/early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 rescue medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 rescue medications, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FU-TS = follow-up total set.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Quality of Life in Children with Vernal Keratoconjunctivitis Questionnaire

Overall, an improvement in the QUICK questionnaire score was only observable in the symptoms domain in subgroup B patients.

Table 22: Change From Baseline (Four Months) in QUICK Questionnaire Scores at Month 12 – Subgroup B

	Subgroup B					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 29)	Vehicle (Placebo) (N = 13)	Total (N = 42)	Twice-Daily Regimen (N = 25)	Vehicle (Placebo) (N = 17)	Total (N = 42)
Symptoms domain						
Month 12/early termination						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	–3.4	[redacted]	[redacted]	–2.8
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily activities domain						
Month 12/early termination						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	0.7	[redacted]	[redacted]	1.2
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SD = standard deviation.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Table 23: Change From Baseline (Four Months) in QUICK Questionnaire Scores at Month 12 – Subgroup C

	Subgroup C					
	Four-Times-Daily Regimen in Period 2			Twice-Daily Regimen in Period 2		
	Four-Times-Daily Regimen (N = 20)	Vehicle (Placebo) (N = 6)	Total (N = 26)	Twice-Daily Regimen (N = 20)	Vehicle (Placebo) (N = 6)	Total (N = 26)
Symptoms domain						
Month 12/early termination						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily activities domain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12/early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; SD = standard deviation.

Source: Clinical Study Report: NVG09B113. A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled study to assess the efficacy and safety of NOVA22007 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered in paediatric patients with active severe vernal keratoconjunctivitis with severe keratitis [CONFIDENTIAL internal manufacturer's report]. Evry (FR), Santen SAS.[1]

Harms

From the start of the study to month 12, a total of 122 (44.7%) patients had at least one adverse event. One additional SAE was recorded in a patient with phimosis in the four-times-daily treatment regimen group. No death was recorded, and no additional AEs of interest were reported.

Critical Appraisal

The extension phase of VEKTIS allowed patients, in consultation with the investigator, to continue taking cyclosporine 0.1% continuously, to continue taking it intermittently, or to stop taking it, within their assigned regimen. The aim of period 2 of VEKTIS was to collect information regarding the long-term (at 12 months) safety and efficacy of cyclosporine 0.1% in patients with severe VKC. The design of period 2 allowed the collection of uncontrolled descriptive statistics. Mean changes in efficacy scores were based on the month 4 results.

The break in randomization, lack of a control group, and descriptive nature of the collected information prevents the application of any statistical inference from the observed results to Canadian clinical settings. However, long-term efficacy and safety information can provide valuable information regarding potential implementation issues, potential safety concerns, and signals of serious failure.

Discussion

Summary of Available Evidence

One DB, triple-arm, parallel-group, phase III RCT met the criteria for inclusion in the CDR systematic review. VEKTIS (N = 169) randomized patients (1:1:1) to one of two cyclosporine 0.1% arms (four times daily or twice daily) or to placebo. Patients received the study treatment for four months, at which point the primary outcome was assessed and an eight-month safety follow-up period began. Patients randomized to the placebo group were switched to one of the two active treatment groups in a 1:1 ratio and continued treatment until they stopped experiencing VKC symptoms or to the end of the study. The primary objective of the study was to compare the efficacy of two different dosing regimens of cyclosporine 0.1% versus placebo on both the evolution of severe keratitis and the need for rescue medication.

Interpretation of Results

Efficacy

VEKTIS enrolled patients with severe VKC as defined by a set of inclusion criteria that included VKC consistent with grade 3 or 4 on the Bonini scale and severe keratitis consistent with grade 4 or 5 on the modified Oxford scale. The primary end point of VEKTIS was the average of the four calculated composite efficacy scores at each month. The composite efficacy outcome was calculated using the following formula:

$Composite\ efficacy\ score\ at\ month\ X$ = corneal fluorescein staining $score\ (baseline)$ – corneal fluorescein staining $score\ (month\ X)$ + $penalty(ies)$

Penalties of –1 were assigned to patients using corticosteroids or who developed corneal ulceration. A positive value in the patient composite efficacy score indicates improvement.

The primary outcome in VEKTIS shows that cyclosporine 0.1% was statistically significantly better than placebo in both treatment regimen groups, with a between-group difference of 0.76 in the least squares mean for the four-times-daily treatment regimen group versus the placebo group (95% CI, 0.26 to 1.27, *P* = 0.007) and a between-group difference of 0.67 in the least squares mean for the twice-daily treatment regimen group versus the placebo group (95% CI, 0.16 to 1.18, *P* = 0.01).

However, a challenge in interpreting these results is to understand the clinical relevance of the composite efficacy outcome. There is no established validity or MCID for this outcome. In addition, the manufacturer calculated the CFS score using the modified Oxford scale, a tool that is also not validated for patients with VKC. The lack of a validity measure makes it difficult to assess the generalizability of the treatment effect to Canadian clinical practice. Also, with the placebo-based comparison, and the lack of any indirect comparison, we are not able to extrapolate the results of the treatment difference versus placebo to the comparators of interest identified in the CDR review protocol. A breakdown of the components that drove the primary outcome indicated that the major contributor was improvement in the CFS score. It was also noted that the corneal ulceration component had little influence on the primary outcome. Secondary outcomes reported in VEKTIS included clinically relevant outcomes, but were not adjusted for multiplicity. However, there is a consistent effect where the four-times-daily regimen of cyclosporine 0.1% was better than placebo at all assessed outcomes. Therefore, results of these secondary outcomes suggest a tangible clinical benefit of cyclosporine 0.1% four times daily. Patients in the twice-daily regimen group also showed consistent improvements over placebo, but not at all monthly assessment visits. Reported outcomes in the follow-up period did not show signs of serious failure or lack of response maintenance.

According to the consulted clinical experts, patients enrolled in VEKTIS were representative of the patients they see with severe VKC. The clinical experts reported that most of their patients with severe VKC would be eligible to enroll in VEKTIS if the inclusion and exclusion criteria were applied to them. In addition, the duration of treatment until the assessment of the primary outcome reflected the seasonal nature of VKC. One area where the settings in VEKTIS would be different in clinical practice is adherence to treatment. Clinical experts reported that patients in the VKC age group have treatment adherence challenges. The clinical experience indicates that adolescents and patients with abating and improving symptoms are the most challenging group in terms of treatment adherence. In contrast, VEKTIS reported acceptable adherence among all enrolled patients.

Concerns that may have biased the results in favour of the four-times-daily treatment regimen group are a potential imbalance in the severity of patients' symptoms between groups, an imbalance in the discontinuation rate, and the use of the heterogenous single imputation method. Baseline characteristics indicate that patients enrolled in the four-times-daily treatment regimen group had more severe disease than those enrolled in the placebo group. Considering the previous dose-finding, phase II study conducted by the manufacturer (which showed better response to cyclosporine 0.1% in patients with severe VKC compared with those with moderate VKC[16]), it is reasonable to assume that this imbalance may bias the results in favour of the four-times-daily treatment regimen group. Baseline severity was included as a covariate in the analysis of the primary outcome, which may address this bias; however, including this as a covariate also complicates the interpretation of the model results, because this variable is also a component of the composite outcome. In addition, at the request of Health Canada, the manufacturer submitted an analysis stratified by severity. This did not lead Health Canada to consider the

severity at baseline as a confounding factor in VEKTIS. As a result, it was not possible to draw a conclusion regarding the existence of a confounding effect. The planned imputation method varied between worst observation carried forward, best observation carried forward, last observation carried forward, and the average of neighbouring observations based on the reason for missing data. This may have led to worse patient outcomes in the placebo group compared with the four-times-daily regimen group due to differences in the discontinuation rate. Sensitivity analysis using observed data only is not sufficient due to the higher discontinuation rate in the placebo group versus the four-times-daily group, which suggests the missing data were not missing completely at random. Due to the limitations in the approach to dealing with missing data, the reported differences from the primary analysis likely overestimate the true effect of the treatment groups, and the single imputation approach underestimate the variance for these estimated differences.

VEKTIS provided a measure of HRQoL by using the QUICK questionnaire as a secondary outcome. The questionnaire was specifically developed for patients with VKC; there is some evidence for validity and reliability for the original Italian version. No measure for the instrument responsiveness or an MCID exists. The outcome was not adjusted for multiplicity and the results of the QUICK questionnaire domains are strongly skewed to the right, which may have limited the value of the analysis of the difference between the results of the active and control arms. Numerically, patients in the cyclosporine 0.1% arms showed better results than those in the control arm. However, it is likely that the limitations identified earlier in the imbalance of severity, discontinuation rates, and missing data imputation methods biased the results in favour of the four-times-daily arm. It is unclear how the differences between the active groups and the control group would translate to patients in Canadian clinical practice settings.

Although this is the first commercially available medication specifically indicated for patients with VKC, clinical experience with cyclosporine for patients with VKC has been available for many years, most commonly through compounding pharmacies. Clinical experts consulted for this review clearly prefer cyclosporine as a treatment option for patients who would otherwise require prolonged or high-dose exposure to corticosteroids to control the symptoms and signs of VKC. Existing clinical experience with cyclosporine has been positive; the main challenge has concerned adherence, especially in cases were there may be an intolerable stinging sensation with the use of the drops.

Harms

Over the full period of the study, 58.0%, 54.5%, and 50.0% of enrolled patients in the four-times-daily regimen, twice-daily regimen, and placebo groups (switched to either group during follow-up), respectively, experienced at least one AE. While the stinging sensation was not explicitly reported, the manufacturer reported that, during the DB phase, “instillation site pain” was reported by six patients (10.5%) in the four-times-daily treatment regimen group, by three patients (5.6%) in the twice-daily treatment regimen group, and by two patients (3.4%) in the placebo group. Over the entire study period, there were four SAEs not deemed to be related to the medication. No deaths were reported.

Conclusions

One DB, phase III RCT met the criteria for inclusion in the CDR systematic review. VEKTIS (N = 169) compared the efficacy of two cyclosporine 0.1% arms (four times daily or twice daily) with placebo, based on the average of four months composite efficacy outcome, each calculated by subtracting the difference in CFS score (using the modified Oxford score), with penalties added for the use of rescue medication and the occurrence of corneal ulceration. Cyclosporine 0.1% was statistically significantly better than placebo using both treatment regimens, with a between-group difference of 0.76 in the least squares mean for the four-times-daily treatment regimen group versus the placebo group (95% CI, 0.26 to 1.27, *P* = 0.007) and a between-group difference of 0.67 in the least squares mean for the twice-daily treatment regimen group versus the placebo group (95% CI, 0.16 to 1.18, *P* = 0.01). However, the clinical significance of these findings remains unknown due to the lack of established MCIDs. Other concerns for bias in these results include a potential imbalance in patient symptom severity between groups, an imbalance in the discontinuation rate, and insufficient adjustment for bias due to missing data. Secondary outcomes were not adjusted for multiplicity, but have shown results similar in direction to the primary outcome. No conclusion could be drawn with regard to the efficacy results of the follow-up period due to the lack of a control arm. Safety data from the DB and follow-up phases did not demonstrate any notable SAEs.

According to the consulted clinical experts, patients enrolled in VEKTIS were representative of patients they see with severe VKC. The clinical trial settings in VEKTIS may have contributed to the high rates of adherence reported in the trial. However, clinical experts identified adherence as a potential implementation challenge in some patients. The clinical experts consulted for this review believe it is an option for patients who may require prolonged or high-dose exposure to corticosteroids to control the symptoms and signs of VKC.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 19, 2019
Alerts:	Biweekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type.
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	Cyclosporine/
2	(verkazia* or ciclosporin* or cyclosporin* or ramihyphin* or abrammune* or arpimune* or cicloral* or cipol* or consupren* or equoral* or gengraf* or imusporin* or neoplanta* or neoral* or optimmune* or papilock* or ikervis* or restasis* or sandimmun* or sangcya* or seciera* sigmasporin* or microoral* or zinograf* or cequa* or aqua-stasis* or cyclo-derm* or s-neoral* or CyA-NOF* or csaneoral* or NOVA 22007 or NOVA22007 or debio088 or "debio 088" or 83HN0GTJ6D or UNII83HN0GTJ6D or "79217600" or "59865133" or CCRIS 1590 or DRG-0275 or OL 27-400 or OL 27400 or sang 35 or sang35 or 7481F1 or HSDB 6881 or "290193" or NSC290193 or SDZ-OXL-400 or CyclASol*).ti,ab,kf,ot,hw,rn,nm.
3	1 or 2
4	conjunctivitis, allergic/ or exp keratoconjunctivitis/
5	(keratoconjunctivit* or blepharokeratoconjunctiv* or (spring adj2 catarrh*) or VKC).ti,ab,ot,kf.
6	((spring or allerg* or vernal or atopic or papillary) adj3 conjunctiv*).ti,ab,ot,kf.
7	or/4-6
8	3 and 7
9	8 use medall
10	*cyclosporine/
11	(verkazia* or ciclosporin* or cyclosporin* or ramihyphin* or abrammune* or arpimune* or cicloral* or cipol* or consupren* or equoral* or gengraf* or imusporin* or neoplanta* or neoral* or optimmune* or papilock* or ikervis* or restasis* or sandimmun* or sangcya* or seciera* sigmasporin* or microoral* or zinograf* or cequa* or aqua-stasis* or cyclo-derm* or s-neoral* or CyA-NOF* or csaneoral* or NOVA 22007 or NOVA22007 or debio088 or "debio 088" or "79217600" or "59865133" or CCRIS 1590 or DRG-0275 or OL 27-400 or OL 27400 or sang 35 or sang35 or 7481F1 or HSDB 6881 or "290193" or NSC290193 or SDZ-OXL-400 or CyclASol*).ti,ab,kw,dq.
12	10 or 11
13	exp keratoconjunctivitis/ or exp allergic conjunctivitis/
14	(keratoconjunctivit* or blepharokeratoconjunctiv* or (spring adj2 catarrh*) or VKC).ti,ab,kw,dq.
15	((spring or allerg* or vernal or atopic or papillary) adj3 conjunctiv*).ti,ab,kw,dq.
16	or/13-15
17	12 and 16
18	17 use oemezd
19	(conference abstract or conference review).pt.
20	18 not 19
21	9 or 20
22	remove duplicates from 21

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Verkazia, NOVA22007, cyclosporine, ciclosporin
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Verkazia, NOVA22007, cyclosporine, ciclosporin

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	June 9-14, 2019
Keywords:	Verkazia, cyclosporine, ciclosporin, NOVA22007, keratoconjunctivitis
Limits:	none

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals.

Appendix 2: Excluded Studies

Table 24: Excluded Studies

Reference	Reason for Exclusion
Hashemian, M. H., et al. (2004). "Comparative clinical trial of topical cyclosporine A and mitomycin C for the management of refractory vernal keratoconjunctivitis." Asian Journal of Ophthalmology **6**(1): 7-12.	Intervention
Yildiz, A. A. and Y. Bardak (2011). "Short term results of topical cyclosporin A in patients with vernal keratoconjunctivitis." Asim, Allerji, Immunoloji **9**(2): 79-85.	Intervention
Ebihara, N., et al. (2009). "A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis." Journal of Ocular Pharmacology and Therapeutics **25**(4): 365-372.	Intervention
Gupta, V. and P. K. Sahu (2001). "Topical cyclosporin A in the management of vernal keratoconjunctivitis." Eye **15**(Pt 1): 39-41.	Intervention
Laibovitz, R. A., et al. (1993). "Pilot trial of cyclosporine 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca." Cornea 12(4): 315-323.	Intervention
Lambiase, A., et al. (2011). "Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study." Journal of Allergy and Clinical Immunology 128(4): 896-897.e899.	Population
Tesse, R., et al. (2010). "Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children." Pediatric Allergy and Immunology **21**(2 Pt 1): 330-335.	Intervention

Appendix 3: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures in Table 25 and review their measurement properties (validity, reliability, responsiveness to change, and minimal clinically important difference).

Table 25: Outcome Measures Included in VEKTIS

Outcome Measure	VEKTIS
Bonini clinical grading scale	Used to determine the study population
Composite primary end point	Primary end point
Modified Oxford staining scale	Part of the composite primary end point; secondary end point
QUICK questionnaire	Secondary end point

QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis; VEKTIS = VErnal KeratoconjunctiviTIs Study.

Findings

Table 26: Summary of Outcome Measures and Their Measurement Properties

Outcome Measure	Type	Conclusions About Measurement Properties	MCID
Bonini clinical grading system	Clinical grading system for severity of vernal conjunctivitis, made up of six main categories	No evidence was found for the validity, reliability, or responsiveness of the clinical grading system.	Not identified
Composite primary end point	Determined by improvement in the modified Oxford staining scale score, with penalties applied for use of rescue therapy or occurrence of corneal ulceration	No evidence was found for the validity, reliability, or responsiveness of the composite primary end point.	Not identified
Modified Oxford grading system	The original Oxford grading system was developed to quantify the amount of epithelial surface damage in patients with dry eye. Following the instillation of a dye, the eye is assessed using a slit lamp and compared with a panel of illustrations representing various degrees of severity of corneal staining. The original grading system consists of six grades; the modified version includes one additional grade.	No evidence was found for the validity, reliability, or responsiveness of the original or modified versions of the Oxford grading system in patients with vernal keratoconjunctivitis.	Not identified
QUICK questionnaire	Self-reported, 16-item questionnaire composed of two domains (symptoms and daily activities) for measuring HRQoL in children from five years to 12 years of age with allergic conjunctivitis,	**Validity:** Convergent validity of the QUICK symptom domain score was demonstrated through weak to strong correlations with five of six clinical sign scores and total clinical sign score. It was also demonstrated through strong correlations with the physical well-being and disease	Not identified

Outcome Measure	Type	Conclusions About Measurement Properties	MCID
	keratoconjunctivitis, or both. Each item is rated on a 3-point Likert-type scale.	domain scores of the KINDL, a generic HRQoL tool. Convergent validity of the QUICK daily activities domain score was shown through a moderate correlation with the KINDL disease domain score. The QUICK questionnaire was originally developed and validated in Italian; evidence for validity of versions in other languages was not found. **Reliability:** Each of the QUICK questionnaire domain scores demonstrated acceptable internal consistency reliability. No evidence for inter-rater and test-retest reliability was found. **Responsiveness:** No evidence for the responsiveness of the QUICK questionnaire domain scores was found.	

HRQoL = health-related quality of life; MCID = minimal clinically important difference; QUICK = Quality of Life in Children with Vernal Keratoconjunctivitis.

Bonini Clinical Grading System

While the clinical grading scale developed by Bonini et al. in 2007[3] was not used as an outcome in the VEKTIS study, it was used to assess patient eligibility for the trial. The Bonini grading scale for grading the severity of vernal keratoconjunctivitis (VKC) consists of six main grades:[3]

- Grade 0, quiescent: The disease has been present in the past or recent present, but the patient is free of symptoms. There is no conjunctival hyperemia and no allergic reaction in the cornea. Non-inflamed papillae may be present.
- Grade 1, mild intermittent: Symptoms, such as itching and mild photophobia, are present during the spring season. Symptoms may be present during the day that have short duration and are well tolerated. There is mild hyperemia without corneal involvement. Giant papillae may be present.
- Grade 2A, moderate intermittent: Symptoms are those described in grade 1, but more frequent and disturbing. There may be mild conjunctival secretion and tearing that affect daily activity. Mild to severe papillary reaction and conjunctival hyperemia (without corneal involvement) may be observed.
- Grade 2B, moderate persistent: Conjunctival hyperemia, secretion, and itching are present every day during the season. There may be occasional superficial punctuate keratitis. Mild to severe papillary reaction may be observed.
- Grade 3, severe: Symptoms are present every day. Daily activities are affected by intense itching and photophobia. There is moderate to severe conjunctival hyperemia as well as secretion associated with Horner-Trantas dots. There is superficial punctuate keratitis. Mild to severe conjunctival papillae are common, with injection and swelling.
- Grade 4, very severe: Daily severe itching and photophobia are present with mucous discharge on the ocular surface and between papillae. Superficial keratopathy or corneal erosions and ulceration are common. Horner-Trantas dots and mild to severe papillary reaction with injection and swelling are present.

- Grade 5, evolution: Symptoms are occasional during seasonal periods. There may be conjunctival papillary reaction, although the cornea is spared. There may be evidence of conjunctival fibrosis on the upper tarsal conjunctiva or at the fornix.

The authors also listed possible therapeutic options for each grade.[3] No evidence was found regarding the validity or reliability of the grading system.

Composite Primary End Point

The primary efficacy end point in the VEKTIS study[1] was a composite end point determined by the corneal fluorescein staining (CFS) score, the need for rescue medication, and the occurrence of corneal ulceration during a four-month period. The CFS score was determined using a modified version of the Oxford staining scale (see next outcome in this appendix). The month 4 score subtracted from the baseline score (where a positive value indicated improvement) was used as the starting score. For each course of rescue medication used (dexamethasone 0.1% eye drops), and for each occurrence of corneal ulceration during the four-month period, a single point was deducted from the starting score to yield a penalty-adjusted score. Rescue medication was limited to a maximum of two courses between monthly scheduled visits.

Although the composite end point has not been validated, the rationale provided for using this scale was that it considers signs (keratitis, as assessed by the CFS score), symptoms (as rescue therapy would be used for worsening symptoms), and the use of corticosteroids, which are associated with harms in VKC patients.[8] In its advice to the manufacturer, the European Committee for Medicinal Products for Human Use (CHMP) considered each part of the composite end point to be clinically meaningful and potentially sensitive in detecting an overall treatment effect.[8] CHMP stated that the composite end point could be driven by one of two of the components. For example, corneal ulcers would be expected to occur only rarely, since rescue therapy was available.[8] CHMP recommended that the manufacturer increase the maximum duration allowed for each course of rescue medication or limit the number of courses to ensure that the results were not driven by artificially short courses of rescue medication; the manufacturer implemented the second recommendation.[8] CHMP also recommended sensitivity analyses exploring changes in the penalty weighting for rescue therapy, and noted that giving the same weight to the need for rescue therapy as to the occurrence of corneal ulcer appeared to be unjustified.[8]

Overall, CHMP accepted the composite end point, but stated that consistency in benefit across all three components in addition to the composite score would need to be demonstrated to conclude a benefit of the drug.[8] In addition, secondary end points (including evaluation of symptoms) were expected to be consistent with the primary end point results; responder analyses were also expected to be useful.[8]

Modified Oxford Grading System

The CFS in the VEKTIS study[1] is a modified version of the Oxford grading system. The original Oxford grading system was developed to quantify the amount of epithelial surface damage in patients with dry eye.[17] The Oxford system uses a series of simplified illustrative panels of the ocular surface, with different panels featuring different densities of dots (which represent appearance of staining with a dye).[17] There are six panels lettered A to E (with corresponding dot counts); each grade corresponds to a staining appearance that lies between the severities represented in each panel.[17] The grades are: 0 = absent, I = minimal, II = mild, III = moderate, IV = marked, and V = severe.[17] The eye is examined

under a slit lamp microscope (using consistent magnification and illumination settings) and a dye (fluorescein, rose Bengal, and/or lissamine green) is instilled.[17] The examiner raises the patient's upper eyelid slightly to observe the entire corneal surface.[17] The temporal and nasal conjunctiva are examined as the patient looks nasally and temporally along the horizontal plane, respectively.[17] The examiner then compares the overall appearance of ocular staining with the panels to determine the most representative grade.[17] The modified version of the Oxford grading system used in the VEKTIS study used the numbers 0 to 5 instead of Roman numerals and added a grade of 0.5 corresponding to a severity between the grades of 0 and I on the original scale.[1]

The original Oxford grading system was developed for use in patients with dry eye. Its validity, reliability, and responsiveness in patients with VKC is unknown. The original article describing the system states: *"Because the grading charts used were devised to represent patterns of staining commonly encountered in dry eye, its use is not recommended to quantify staining in other ocular surface disorders."*[17] A rationale was not given for the adaptation of the system to VKC by adding an extra grade, nor was any evidence of validity, reliability, or responsiveness was found for the modified Oxford grading system.

Quality of Life in Children with Vernal Keratoconjunctivitis Questionnaire

The Quality of Life in Children with Vernal Keratoconjunctivitis (QUICK) questionnaire is a self-reported questionnaire for measuring health-related quality of life (HRQoL) in children from five years to 12 years of age who have allergic conjunctivitis, keratoconjunctivitis, or both.[7] The questionnaire is composed of 16 items in two domains: 12 items in the symptoms domain and four in the daily activities domain.[7] Each item is rated on a 3-point Likert scale (1 = never, 2 = sometimes, and 3 = always) according to how often patients have experienced symptoms or difficulties with activities in the past two weeks.[7] A higher score on an item or domain corresponds with worse HRQoL. The raw scores are linearly transformed to a scale ranging from 0 to 100.[7]

The development of the QUICK questionnaire was described in a report by Sacchetti et al. in 2007.[7] The QUICK questionnaire was originally developed in Italian and subsequently translated into English by two independent bilingual translators.[7] Potential items in the QUICK questionnaire were initially generated through: a literature review of existing HRQoL questionnaires in children with ocular surface symptoms, allergies, or both; a panel of four ophthalmologists and two immunologists active in clinical research in the field of ocular allergy who identified symptoms and problems in children with VKC; interviews with 10 children with VKC and their parents to identify areas of daily life affected by VKC; and two psychologists with experience in developing and validating HRQoL questionnaires for allergic diseases, who adapted the items for the pediatric population.[7] The 51 items that were generated were reduced to 42 by removing items that were redundant, ambiguous, difficult to understand, or expressed in the negative form.[7] The items were further reduced by administering the 42 items to 30 children with VKC in the active phase.[7] The patients were asked to rate how often they had experienced each item in the preceding two weeks on a 3-point scale (1 = never, 2 = sometimes, and 3 = always). The highest scoring 30 items were used to form a new scale for validation.[7]

The 30-item version of the QUICK questionnaire was administered to 41 children with active VKC aged five years to 12 years.[7] Among these patients, 34 were receiving anti-allergic eyedrops, three were receiving cyclosporine A eyedrops, and four were not receiving topical treatment.[7] Convergent validity was assessed by administering the KINDL questionnaire (one of two versions, depending on age) to 24 of the patients and by scoring

six clinical signs (conjunctival hyperemia, secretion, chemosis, superficial punctuate keratopathy, limbal papillary reaction, and tarsal papillary reaction) in the whole cohort on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe).[7] The KINDL, a generic tool for assessing HRQoL, consists of six domains (physical well-being, emotional well-being, self-esteem, family, friends, and school) and one domain for chronically ill children.[7] A higher score on the subscales of the KINDL questionnaire corresponds to higher HRQoL.[7] For the clinical signs, a total sign score was calculated by summing the individual sign scores (range of 0 to 18).[7]

Factor analysis of the item scores revealed two dimensions. The QUICK questionnaire was then reduced to its final version, consisting of 16 items, by eliminating items outside the two dimensions.[7] The internal consistency reliability of each domain, assessed using the Cronbach correlation coefficient (alpha), was acceptable for group comparisons (alpha ≥ 0.70[18]).[7] According to Spearman's rank correlation coefficient (rho), the QUICK symptom domain score was strongly correlated (magnitude of rho > 0.50[19]) with the clinical signs of conjunctival hyperemia (rho = 0.656; $P < 0.001$) and superficial punctuate keratopathy (rho = 0.657; $P < 0.001$), and moderately correlated (magnitude of rho from 0.30 to 0.50[19]) with the clinical signs of secretion (rho = 0.409; $P = 0.042$), chemosis (rho = 0.469; $P = 0.012$), and limbal papillary reaction (rho = 0.387; $P = 0.042$) as well as the total clinical sign score (rho = 0.442; $P = 0.010$).[7] The QUICK symptom domain score was not significantly correlated with tarsal papillary reaction or duration of disease, nor was the daily activity domain score significantly correlated with the clinical sign scores.[7] Of the seven measured domains of the KINDL, physical well-being was strongly correlated with the QUICK symptom domain score (Pearson correlation coefficient [R] = –0.635, $P = 0.006$), while the disease domain was strongly correlated with the QUICK symptom domain score (R = –0.699, $P = 0.001$) and the QUICK daily activities domain score (R = –0.526, $P = 0.012$).[7]

A separate study by Leonardi et al. in 2008 evaluating a new scoring system (the vernal keratoconjunctivitis – Collaborative Longitudinal Evaluation of Keratoconus study [VKC-CLEK]) for assessing epithelial damage in patients with VKC compared the new scoring system with a single score for the QUICK questionnaire, presumably a total score combining the two domains.[20] A higher VKC-CLEK score (range of ordinal scores of 0 to 8), based on fluorescein and lissamine green corneal staining, indicates more severe epithelial damage.[20] In the study, 25 patients with a mean age of 11 years were assessed using the VKC-CLEK scale, the QUICK questionnaire, and other instruments.[20] The VKC-CLEK and QUICK scores were converted to one of three levels of severity (mild, moderate, or severe) based on an even division of the score ranges into thirds.[20] The categorical QUICK results were then compared with the VKC-CLEK and Oxford staining scores using Cohen's kappa coefficient (the method of converting to categories in the latter scale was not described).[20] While agreement percentages of 66% and 22% were found for the QUICK categorical score versus the VKC-CLEK and Oxford scores, respectively, there was either no agreement or poor agreement[21] (kappa = –0.076 and kappa = 0.018, respectively).[20]

Some limitations of the validation study for the QUICK questionnaire affect the ability to interpret the domain scores. The QUICK questionnaire was not administered as the 16-item final version in the validation study, and the questionnaire was validated in Italian, with no evidence for validity in other languages. Inter-rater reliability, test-retest reliability, and responsiveness were not evaluated in the validation study, nor was the minimal clinically important difference established. Details on how the questionnaire was administered and how patients provided responses were not outlined in the validation study.

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