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A Randomized, Controlled Trial of Cyclosporine A Cationic Emulsion in Pediatric Vernal Keratoconjunctivitis

The VEKTIS Study

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Purpose: Vernal keratoconjunctivitis (VKC) is a chronic, allergic, and potentially severe ocular disease affecting children and adolescents that can lead to impaired quality of life (QoL) and loss of vision. This study evaluated the efficacy and safety of an investigational therapy for severe VKC, cyclosporine A (CsA) cationic emulsion (CE), an oil-in-water emulsion with increased bioavailability versus conventional CsA formulations.

Design: The VErnal KeratoconjunctiviTIs Study (VEKTIS) is a phase 3, multicenter, double-masked, vehicle-controlled trial.

Participants: Pediatric patients (4 to younger than 18 years) with active severe VKC (grade of 3 or 4 on the Bonini severity scale) and severe keratitis (corneal fluorescein staining [CFS] score of 4 or 5 on the modified Oxford scale).

Methods: One hundred sixty-nine patients were randomized to CsA CE 0.1% (1 mg/ml) eye drops 4 times daily (high dose), CsA CE twice daily (low dose) plus vehicle twice daily, or vehicle 4 times daily for 4 months.

Main Outcome Measures: The primary end point was a mean composite score that reflected CFS, rescue medication use (dexamethasone 0.1% 4 times daily), and corneal ulceration over the 4 months.

Results: Differences in least-squares means versus vehicle for the primary end point were statistically significant for both the high-dose (0.76; $P = 0.007$) and the low-dose (0.67; $P = 0.010$) groups, with treatment effect mainly driven by CFS score. Significant differences were found between both active treatment groups and vehicle for use of rescue medication. Vernal keratoconjunctivitis symptoms and patient QoL (assessed by visual analog scale and the Quality of Life in Children with Vernal Keratoconjunctivitis questionnaire) improved in all 3 groups, with significant improvements for high-dose CsA CE versus vehicle.

Conclusions: The efficacy of high-dose CsA CE in improving keratitis, symptoms, and QoL for those with severe VKC was demonstrated in these study patients. In addition, in this study cohort, CsA CE was well tolerated. *Ophthalmology 2019;■:1–11* © *2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Vernal keratoconjunctivitis (VKC) is a severe and potentially debilitating ocular allergic disease that typically occurs in temperate zones such as the Mediterranean area, the Middle East, Africa, Central America, and the Indian subcontinent and less frequently in Northern Europe, North America, and Australia.[1–3] Vernal keratoconjunctivitis is an orphan disease, with prevalence estimated at 3.2 per 10 000 inhabitants (0.03%) in the European Union.[1]

Vernal keratoconjunctivitis is characterized by allergic inflammation of the ocular surface, with clinical manifestations involving the tarsal (palpebral) and/or bulbar conjunctiva that can have a seasonal course, but also may be chronic with acute exacerbations.[4] Key signs and symptoms of VKC include photophobia, conjunctival hyperemia, itching, stringy mucous discharge, giant papillae on the upper tarsal conjunctiva, papillae and gelatinous infiltrates on the limbus with white-yellow nodules (Horner-Trantas dots), superficial punctate keratitis, and corneal shield ulcers.[4–6] Complications from corneal involvement include persistent keratitis and corneal ulceration, which in turn may result in corneal scarring, thinning, and visual loss.[7] Corneal complications and keratitis are estimated to occur in 25% to 50% of patients.[1]

Vernal keratoconjunctivitis typically occurs in school-age children, with an age of onset before 10 years in 80% of cases (typical range, 4–7 years), and is reported in males

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3 to 4 times more often than in females.[1,6] Vernal keratoconjunctivitis often resolves after puberty, although it may persist in adulthood, where the male-to-female ratio is closer to 1:1.[4,6] Children with severe VKC may have a poor quality of life (QoL) because of limitations in daily activities, schooling, and vacationing as well as potential psychological and relationship issues.[1,6,8]

The immunopathogenesis of VKC is thought to involve a Th2-mediated allergic mechanism in which Th2-derived cytokines drive immunoglobulin E production and activation of mast cells, eosinophils, neutrophils, and possibly resident cells, including corneal keratocytes and conjunctival fibroblasts, with subsequent release of a myriad of toxic mediators that promote inflammatory and remodeling processes.[3,6,9,10]

Several classes of pharmacologic agents are available for the treatment of VKC, including topical mast-cell stabilizers, antihistamines, dual-acting agents with both mast-cell stabilizing and antihistaminic activity, and nonsteroidal anti-inflammatory agents. These agents offer short-term relief but do not effectively address the complex immune response that initiates and perpetuates the allergic ocular inflammation, especially in moderate to severe VKC.[4,11] Topical corticosteroids often are necessary in moderate to severe disease; although effective, they must be used for short courses because of their tendency to promote severe adverse effects such as cataracts, glaucoma, and secondary corneal infections.[1,4] Topical cyclosporine A (CsA) is effective in controlling ocular surface inflammation in VKC and is thought to work by inhibiting Th2 proliferation and interleukin 2 production and by reducing levels of immune cells and mediators acting on the ocular surface and conjunctiva.[11] In clinical studies, CsA has been shown to reduce signs and symptoms of VKC while providing a steroid-sparing effect.[12–16]

As a lipophilic substance, CsA is practically insoluble in water and must be delivered topically to the eye in a lipid-based system.[17] Cyclosporine A cationic emulsion (CE) 0.1% (1 mg/ml) is a CsA formulation developed for topical treatment of severe forms of immune-mediated ocular diseases.[18] When a cationic emulsion is instilled in the eye, the positively charged nanodroplets are attracted to the negatively charged cell membranes, resulting in increased residence time at the ocular surface; thus, CsA CE provides a vehicle for improved ocular bioavailability of CsA.[19] Previous studies have demonstrated the safety and efficacy of CsA CE in treating severe keratitis in dry eye.[20–22] Cyclosporine A CE also has been shown to provide a significant reduction of VKC signs during a 4-week treatment period, particularly in patients with severe keratitis (Santen, data on file, 2007). The phase 3 VEKTIS study was designed to compare the efficacy and safety of 2 different dosing regimens of CsA CE versus the CE vehicle in children and adolescents with severe VKC.

Methods

Study Design

VEKTIS was a multicenter, randomized, double-masked, vehicle-controlled, parallel-arm phase 3 study conducted from April 29, 2013, through February 1, 2016, at 51 sites in 11 countries (Spain, France, India, Italy, Israel, United States, Greece, Hungary, Portugal, Croatia, and Germany). The study was conducted in accordance with the tenets of the Declaration of Helsinki and was in compliance with International Conference on Harmonisation guidelines of Good Clinical Practice and applicable local ethical and legal requirements. Independent ethics committees and regulatory agencies (as appropriate) approved the study protocol before study initiation (see Appendix [available at www.aaojournal.org] for further details). The parents or legal guardian of each patient provided written informed consent, and the patient provided assent when possible. The study was registered prospectively with ClinicalTrials.gov (identifier, NCT01751126).

The study included a 4-month efficacy and safety evaluation period and an 8-month safety follow-up period (Fig 1). Only data from the 4-month treatment period comparing the study drug versus vehicle are reported herein. On day 0, eligible patients with severe VKC were assigned randomly in a 1:1:1 ratio to receive 1 drop of CsA CE 0.1% (1 mg/ml) 4 times daily (high dose), 1 drop of CsA CE twice daily (low dose) plus 1 drop of vehicle twice daily, or 1 drop of vehicle 4 times daily. Treatment assignments were generated using a computerized randomization schema, stratified by country, and centralized using an interactive web-response system.

Patients and caregivers were educated regarding the optimal technique for ophthalmic drop instillation and were instructed to instill 1 drop of their assigned study medication into the lower conjunctival sac of each eye in the morning, at noon, in the afternoon, and in the evening, approximately 4 hours apart. Patients were provided with single-dose containers, each yielding 2 drops of study medication (1 drop for each eye). Study visits were scheduled every 4 weeks during the efficacy evaluation period.

During the study, rescue medication (dexamethasone 0.1% 4 times daily for up to 5 days) was permitted in the event of keratitis (corneal fluorescein staining [CFS] score based on modified Oxford scale[23]; 7-point scale, range, 0–5 [absence of staining to greatest severity]; individual grades: 0, 0.5, 1, 2, 3, 4, and 5) worsening by 1 grade or more or maintenance of the CFS score for 2 months at the entry level, symptom worsening of 10 mm or more for 1 or more of the 4 VKC symptoms plus worsening or maintenance at the entry level of the mean visual analog scale (VAS) score for the 4 symptoms, or both. Dexamethasone had to be given at least 30 minutes before or after study medication. A maximum of 2 courses were allowed between study visits.

Patients

Eligible patients included males or females 4 to younger than 18 years of age with active severe VKC (grade 3 or 4 on the Bonini scale[24]) and severe keratitis with a CFS score of grade 4 or 5 on the modified Oxford scale. Patients were required to have experienced 1 or more recurrences of VKC during the previous year and to have a mean score for the 4 main VKC symptoms (photophobia, tearing, itching, and mucous discharge) of 60 mm or more on a 0- to 100-mm VAS (0, no symptoms; 100, comparable with the worst discomfort ever experienced). Enrollment had to occur early during the allergy season for that site to allow the 4-month treatment period to occur during the VKC season.

Patients were excluded if they demonstrated ocular anomalies other than VKC affecting the ocular surface; abnormalities of lid anatomic features, nasolacrimal drainage, or blinking function; active ocular infection or history of ocular herpes, varicella zoster or vaccinia virus infection; or any ocular disease that would require topical ocular treatment during the study. Presence or history of severe systemic allergy at study entry also was an exclusion criterion. Patients were not tested with a skin prick test; nor were they required to have a specific immunoglobulin E blood level as part of the inclusion criteria. Topical or systemic corticosteroids within 1

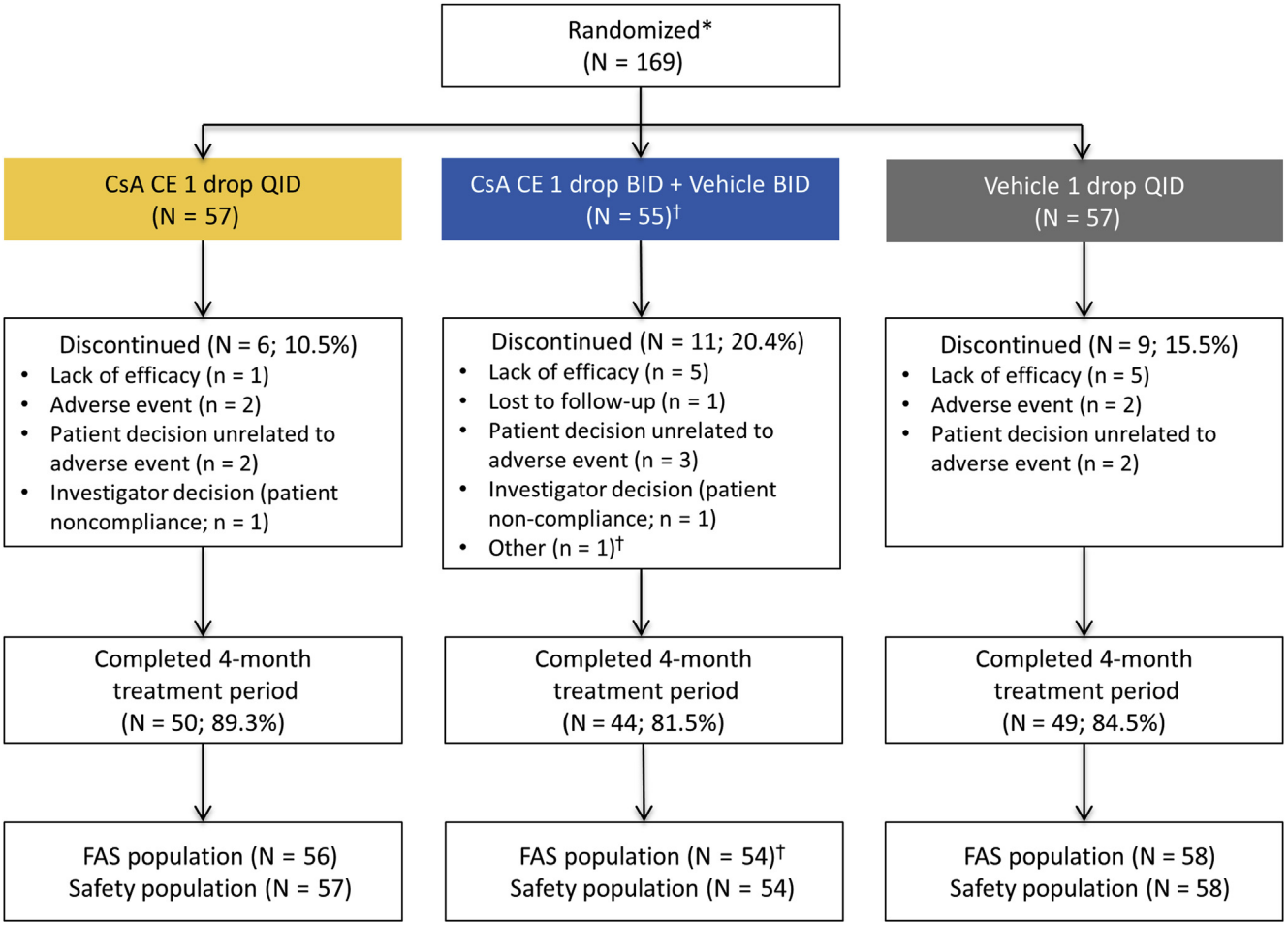

Figure 1. Flowchart showing patient disposition during the 4-month treatment period. *One patient was randomized to cyclosporine A (CsA) cationic emulsion (CE) 0.1% (1 mg/ml) 1 drop 4 times daily but incorrectly received vehicle initially; 1 patient randomized to CsA CE 1 drop twice daily plus vehicle twice daily received CsA CE 1 drop 4 times daily during part of the study period and was analyzed for safety in the high-dose group. †One randomized patient did not have severe active vernal keratoconjunctivitis (VKC) at baseline and was excluded from the full analysis set (FAS). BID = twice daily; QID = 4 times daily.

week; topical CsA, tacrolimus, or sirolimus or any systemic immunosuppressive drug within 90 days before enrollment; scraping of the vernal plaque within 1 month; or any other ocular surgery within 6 months before baseline were not allowed.

Efficacy Assessments

Efficacy was assessed monthly during the 4-month treatment period using a composite score designed to reflect changes in 3 important aspects of the VKC disease process that are known to have a major impact on symptoms and disease progression: (1) keratitis assessed by CFS and scored using the modified Oxford scale (a sign of allergic inflammatory damage to the ocular surface, which impacts the main symptoms of photophobia, burning, and pain)[6–10]; (2) need for rescue medication (a sign of poor response to study treatment); and (3) occurrence of corneal ulceration (a sign of disease worsening and poor response to treatment; defined for the study as an extensive superficial punctate keratitis with exposure of Bowman's membrane). The composite score at each monthly visit was calculated as the difference in CFS score from baseline, with penalties of −1 for each course of rescue medication or occurrence of corneal ulceration, as follows:

- Patient's score at month X = CFS score (baseline) − CFS score (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).

A positive value indicated improvement. The primary efficacy end point was defined as the mean of the composite scores recorded at the 4 monthly visits.

Secondary efficacy end points assessed at each monthly visit included the CFS score, use of rescue therapy, occurrence of corneal ulceration, VAS scores for the 4 main VKC symptoms, QoL over the preceding 2-week period (assessed using the symptoms and daily activities domains of the Quality of Life in Children with Vernal Keratoconjunctivitis questionnaire),[8] and use of artificial tears (all unpreserved brands permitted) as recorded in the patient diary. In addition, responder rate and the investigator global evaluation of efficacy (IGEE) were assessed at month 4. For the IGEE, the investigator rated the overall effect of study medication using a 4-point scale ranging from 0 (unsatisfactory) to 3 (very satisfactory). Both the VAS and Quality of Life in Children with Vernal Keratoconjunctivitis assessments were performed at the beginning of study visits before a medical history or

any other study-related assessments. A patient was considered a responder if their mean CFS score during the last 3 months of treatment was 50% or less of the baseline value and he or she did not withdraw for a reason possibly resulting from treatment, did not experience ulceration, and did not use rescue medication during the last 3 months of treatment.

Other parameters assessed were conjunctival erythema or hyperemia, conjunctival discharge, conjunctival chemosis, papillae, and limbal infiltrates, each evaluated by external examination and biomicroscopy using a slit lamp and graded on a numerical scale. Numerical scales for conjunctival erythema or hyperemia, conjunctival discharge, conjunctival chemosis, papillae, and limbal infiltrates were constructed as follows. For conjunctival erythema or hyperemia, conjunctival discharge, and conjunctival chemosis, the scores were: 0, absent; 1, mild; 2, moderate; and 3, severe. For papillae, the scores were: 0, absent; 1, mild hyperemic scattered papillae; 2, moderate diffuse hyperemic swollen papillae; 3, as before, but more severe; and 4, hyperemic swollen giant papillae covering the superior tarsal plate. For limbal infiltrates, the scores were: 0, absent; 1, mild limbus hyperemia and swelling; 2, moderate limbus hyperemia and swelling; 3, as before, but more severe; and 4, 360° limbus hyperemia and swelling.

Safety

Local ocular effects were evaluated by external examination and biomicroscopy using a slit lamp. Anterior chamber inflammation and lens opacification were assessed, each graded on a numerical scale (0−3), as described in the Appendix (available at www.aaojournal.org). Ocular and systemic adverse events were monitored throughout the study. Best-corrected distance visual acuity and intraocular pressure by tonometry were assessed at each visit. Blood samples for measurement of CsA levels, serum creatinine, alanine aminotransferase, and aspartate aminotransferase were collected at baseline and months 2 and 4.

Statistical Analysis

Efficacy parameters were evaluated in the full analysis set, which consisted of all randomized patients who received 1 or more doses of study medication and did not experience early withdrawal during the first week for reasons definitely unrelated to study medication (thus resulting in a lack of postrandomization data). For the primary end point, the superiority of CsA CE over vehicle was evaluated using an analysis of covariance model with treatment, baseline CFS, and exposure to VKC season as covariates. A Hochberg procedure was used to address multiplicity issues with the 2 active treatment regimens. Additional information regarding statistical procedures is provided in the Appendix (available at www.aaojournal.org).

Results

Patients

A total of 169 patients were randomized to study treatment (Fig 1). Of these, 143 patients (84.6%) completed the 4-month treatment period. Overall, the most frequent reasons for discontinuation were lack of efficacy (6.5%) and patient decision unrelated to an adverse event (4.1%). Notably, more patients in the CsA CE low-dose and vehicle groups versus the CsA CE high-dose group withdrew early because of lack of efficacy (9.3% and 8.6% vs. 1.8%, respectively). One randomized patient did not have severe active VKC at baseline and therefore was excluded from the full analysis set.

The demographic and baseline clinical characteristics of the 3 treatment groups generally were well balanced (Table 1). Overall, the mean age was 9.2 years, 78.6% of patients were male, and 70.8% were white. The mean time since VKC diagnosis was 3.4 years. Most patients (65.5%) exhibited the mixed form of VKC (both limbal and tarsal signs), with perennial VKC diagnosed in 55.4%. Most demonstrated VKC grade 3 (61.9%) and a CFS score of 4 (86.3%) at baseline (13.7% showed a CFS score of 5). Notably, more patients in the CsA CE high-dose group showed a CFS score of 5 at baseline versus the other 2 groups. Asthma was present in 19.6% of the overall study population.

Composite Efficacy Score (Primary End Point)

The composite efficacy score increased (i.e., improved) over the 4-month treatment period in each treatment group (Fig 2A). The mean composite score over the entire period (primary end point) was 2.06 (95% confidence interval [CI], 1.67−2.45) in the CsA CE high-dose group, 1.93 (95% CI, 1.56−2.30) in the CsA CE low-dose group, and 1.34 (95% CI, 1.02−1.67) in the vehicle group (Fig 2B). Between-group comparisons favored both active treatments over vehicle; the difference in the least-squares mean for CsA CE high-dose versus vehicle was 0.76 (95% CI, 0.26−1.27; $P = 0.007$), and the difference for CsA CE low-dose versus vehicle was 0.67 (95% CI, 0.16−1.18; $P = 0.010$; Table 2).

The CFS score was the main driver of the improvement in the composite primary end point, accounting for 70% and 78% of the treatment effect in the CsA CE high-dose and low-dose groups, respectively (Table 2). Decreases in rescue medication use accounted for most of the remaining treatment effect (30% in the CsA CE high-dose group; 22% in the CsA CE low-dose group). The proportion of patients with 1 or more courses of rescue medication over the 4 months was 32.1%, 31.5%, and 53.4% in the 4 times daily, twice daily, and vehicle groups, respectively, and the mean number of rescue courses was 0.66, 0.69, and 1.31, respectively ($P = 0.010$, high-dose group vs. vehicle; $P = 0.055$, low-dose group vs. vehicle). There was no difference in the mean number of ulcer occurrences per month across treatment groups (0.001 for 4 times daily, 0.003 for twice daily; $P = 0.996$ for both vs. vehicle). The total number of cases of corneal ulceration was 4 (7.0%) in the high-dose group, 3 (5.6%) in the low-dose group, and 3 (5.2%) in the vehicle group. Both active treatments generally were favored over vehicle in terms of the composite efficacy scores across most subgroups defined by patient baseline characteristics (Fig 3).

Other Efficacy End Points

The benefits of CsA CE treatment, particularly in the high-dose group, were evident on most secondary efficacy end points. The 4 key VKC symptoms as measured on the VAS improved over time in each treatment group. The greatest symptom improvement was observed in the CsA CE high-dose group, with the largest symptom decrease seen from baseline to month 1. High-dose CsA CE provided significantly greater symptom improvement versus vehicle at months 1, 2, and 4 for photophobia, at months 2 and 4 for tearing, and at all monthly time points for itching and mucous discharge (Fig 4). Significant improvements with low-dose CsA CE versus vehicle were noted primarily at month 2.

The responder rate was significantly higher in the CsA CE high-dose group (57.1%) and low-dose group (61.1%) versus the vehicle group (34.5%; $P = 0.015$ and $P = 0.004$, respectively). Monthly use of artificial tears was low in all treatment groups, ranging from 1.8% to 7.1% in the CsA CE high-dose group, 0% to 9.3% in the CsA CE low-dose group, and 3.4% to 19.0% in the vehicle group. Quality of life, as measured by the symptoms and daily activities

Table 1. Demographic and Baseline Characteristics of the Full Analysis Set Cohort

Characteristic	Cyclosporine A Cationic Emulsion 0.1% (1 mg/ml) 4 Times Daily (n = 56)	Cyclosporine A Cationic Emulsion 0.1% (1 mg/ml) Twice Daily (n = 54)	Vehicle (n = 58)
Age (yrs), mean (SD)	9.1 (3.3)	9.6 (3.4)	8.9 (3.2)
Age group (yrs), no. (%)			
4–11	43 (76.8)	38 (70.4)	46 (79.3)
12–18	13 (23.2)	16 (29.6)	12 (20.7)
Gender, no. (%)			
Male	44 (78.6)	42 (77.8)	46 (79.3)
Female	12 (21.4)	12 (22.2)	12 (20.7)
Race, no. (%)			
White	40 (71.4)	38 (70.4)	41 (70.7)
Asian	11 (19.6)	11 (20.4)	13 (22.4)
Black	3 (5.4)	5 (9.3)	2 (3.4)
Other	2 (3.6)	0 (0)	2 (3.4)
Form of VKC, no. (%)			
Limbal	8 (14.3)	2 (3.7)	7 (12.1)
Tarsal	15 (26.8)	13 (24.1)	13 (22.4)
Mixed	33 (58.9)	39 (72.2)	38 (65.5)
Type of VKC, no. (%)			
Seasonal	29 (51.8)	25 (46.3)	21 (36.2)
Perennial	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)
VKC grade, no. (%)*			
3	32 (57.1)	32 (59.3)	40 (69.0)
4	24 (42.9)	22 (40.7)	18 (31.0)
CFS score, no. (%)*			
4	42 (75.0)	49 (90.7)	54 (93.1)
5	14 (25.0)	5 (9.3)	4 (6.9)
Asthma, no. (%)	12 (21.4)	10 (18.5)	11 (19.0)

CFS = corneal fluorescein staining; SD = standard deviation; VKC = vernal keratoconjunctivitis.
*Grade or score of analysis eye; VKC grading by Bonini scale and CFS score by modified Oxford scale.

domain scores on the Quality of Life in Children with Vernal Keratoconjunctivitis questionnaire, improved from baseline to month 4 in all treatment groups. The greatest improvements in both domains were observed in the CsA CE high-dose group, with statistical significance versus vehicle demonstrated at most time points (Fig 5). A post hoc analysis at month 4 also revealed that 8 patients (14.3%) in the high-dose group, 4 patients (7.4%) in the low-dose group, and 1 patient (1.7%) of those receiving vehicle

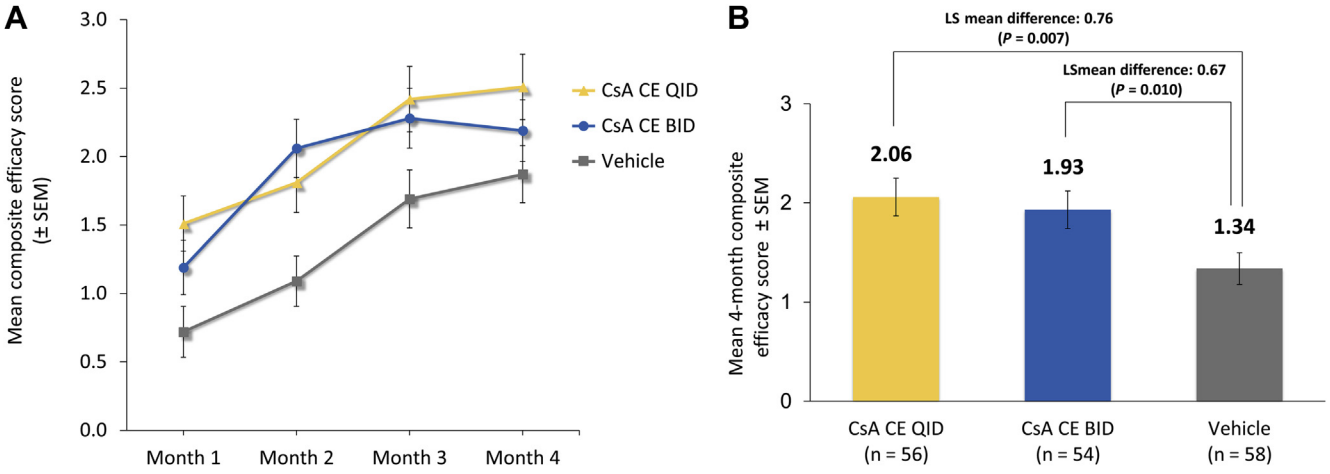

Figure 2. **A**, Graph showing mean composite efficacy score at each visit. **B**, Graph showing mean composite efficacy score over the 4-month treatment period. The composite score at each monthly visit was calculated as the difference in corneal fluorescein staining score from baseline, with penalties of −1 for each course of rescue medication or occurrence of corneal ulceration; a positive value indicated improvement. BID = twice daily; CsA CE = cyclosporine A cationic emulsion 0.1% (1 mg/ml); LS = least-squares; SEM = standard error of the mean; QID = 4 times daily.

Table 2. Analysis of Composite Primary End Point and Its Components

End Point	High-Dose Cyclosporine A Cationic Emulsion 0.1% (1 mg/ml) vs. Vehicle	Low-Dose Cyclosporine A Cationic Emulsion 0.1% (1 mg/ml) vs. Vehicle
Composite efficacy score (primary end point)*		
LS mean (95% CI)	0.76 (0.26−1.27)	0.67 (0.16−1.18)
Adjusted *P* value†	0.007	0.010
Mean CFS score per month (change from baseline)		
LS mean (95% CI)	0.52 (0.11−0.94)	0.53 (0.11−0.94)
Adjusted *P* value†	0.014	0.014
Relative contribution to primary end point (%)	70.3	77.6
Mean no. of rescue medication courses per month		
LS mean (95% CI)	0.22 (0.07−0.37)	0.15 (0.00−0.30)
Adjusted *P* value†	0.010	0.055
Relative contribution to primary end point (%)	29.6	21.9
Mean no. of ulcer occurrences per month		
LS mean (95% CI)	0.001 (−0.04 to 0.04)	0.003 (−0.03 to 0.04)
Adjusted *P* value†	0.966	0.966
Relative contribution to primary end point (%)	0.1	0.5

CFS = corneal fluorescein staining; CI = confidence interval; LS = least-squares.
*The composite score at each monthly visit was calculated as the difference in CFS score from baseline, with penalties of −1 for each course of rescue medication or occurrence of corneal ulceration; a positive value indicated improvement.
†Analysis of covariance model with adjustment through the Hochberg's procedure.

alone demonstrated a VAS score of 0 for the mean of the 4 symptoms, had not experienced ulceration, and had not used rescue medication in the previous 3 months.

For the IGEE, the investigators provided a positive global assessment of study treatment in most patients. At month 4, an IGEE rating of satisfactory or very satisfactory was given for 85.7% of patients in the CsA CE high-dose group, 86.0% of patients in the CsA CE low-dose group, and 68.8% of patients in the vehicle group ($P = 0.080$ for both comparisons of active treatment vs. vehicle).

On slit-lamp examination, there was a shift from baseline to month 4 in the proportion of patients with grade 2 or 3 findings to grade 0 or 1 findings for conjunctival erythema or hyperemia, conjunctival discharge, papillae, limbal infiltrates, and conjunctival chemosis in all treatment groups. The assessment of conjunctival erythema or hyperemia showed a statistically significant difference between the active treatments versus vehicle ($P = 0.017$ and $P = 0.031$, respectively); the proportion with grade 2 to 3 findings decreased from 89.3% at baseline to 25.0% at month 4 in the CsA CE high-dose group, from 87.0% to 22.2% in the CsA CE low-dose group, and from 84.5% to 34.5% in the vehicle group.

Safety

Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity. Treatment-related TEAEs were similar in incidence across treatment groups, except for instillation site pain, which occurred at a higher rate in the CsA CE high-dose group (Table 3). Three patients experienced serious adverse events (severe

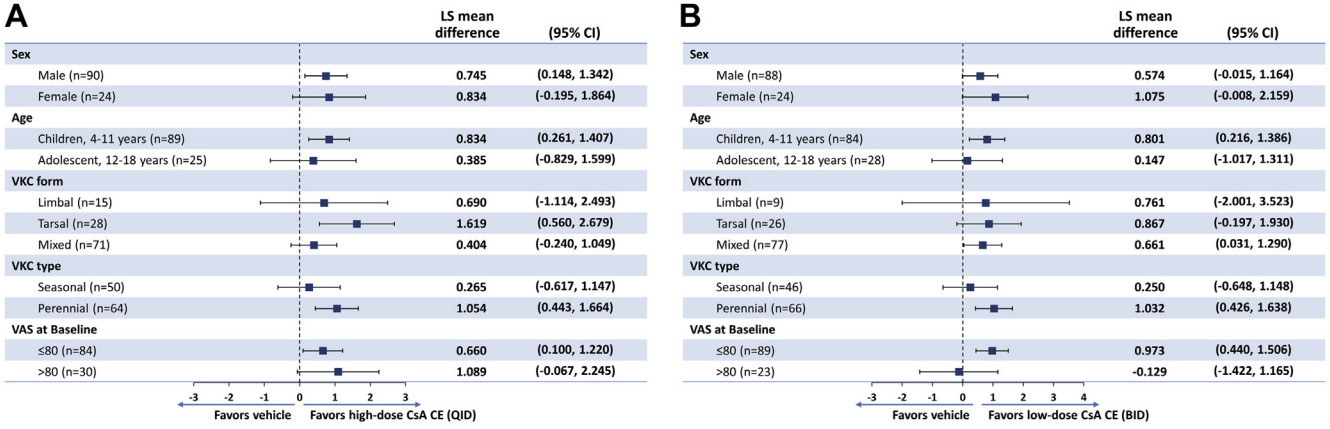

Figure 3. Forest plots showing (**A**) high-dose cyclosporine A (CsA) cationic emulsion (CE) 0.1% (1 mg/ml) 4 times daily and (**B**) low-dose CsA CE (twice daily) versus vehicle alone for the composite efficacy score in key subgroups. The composite score at each monthly visit was calculated as the difference in corneal fluorescein staining score from baseline, with penalties of −1 for each course of rescue medication or occurrence of corneal ulceration; a positive value indicated improvement. BID = twice daily; CI = confidence interval; LS = least-squares; QID = 4 times daily; VAS = visual analog scale; VKC = vernal keratoconjunctivitis.

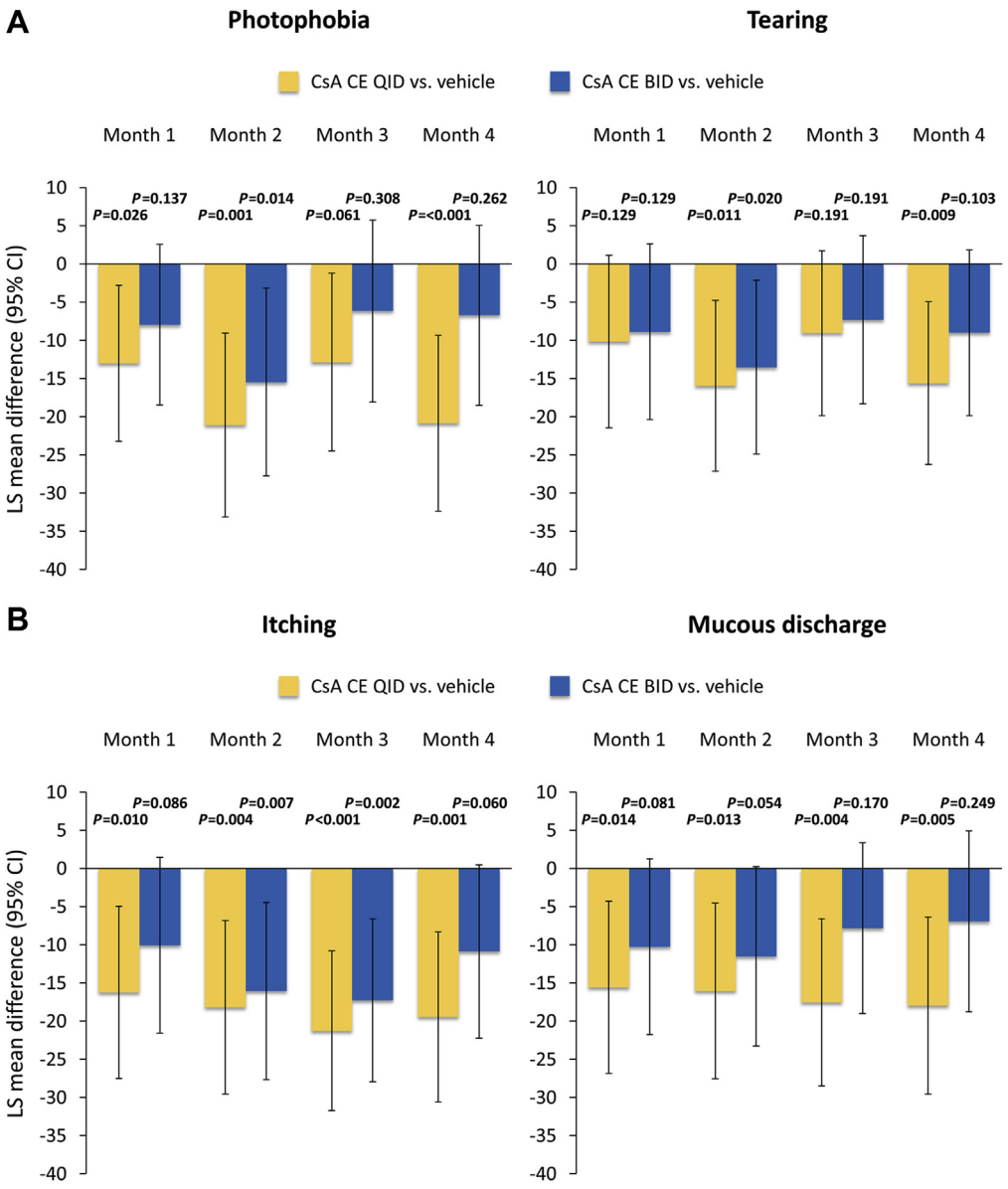

Figure 4. Graphs showing improvement in the visual analog scale (VAS) score (0–100 mm) for the symptoms of (**A**) photophobia and tearing and (**B**) itching and mucous discharge. A decrease in VAS score from baseline indicates improvement. *P* values were derived via linear mixed model for repeated measures with adjustment through the Hochberg's procedure. BID = twice daily; CI = confidence interval; CsA CE = cyclosporine A cationic emulsion; LS = least-squares; QID = 4 times daily.

ulcerative keratitis and tibia fracture in the CsA CE high-dose group, and a head injury in the CsA CE low-dose group); all were considered unrelated to study treatment. There were no clinically relevant changes in alanine aminotransferase, aspartate aminotransferase, creatinine, blood pressure, or pulse or respiratory rates over the 4-month treatment period. At month 4, CsA blood levels were measurable in 14 patients (28.0%) in the CsA CE high-dose group and in 5 patients (10.6%) in the CsA low-dose group. The maximum blood CsA concentration in these groups was 0.670 ng/ml and 0.336 ng/ml, respectively; these amounts are considered to be negligible. Best-corrected distance visual acuity improved over the 4-month treatment period in all treatment groups, most prominently in the high-dose group (mean change from baseline, −0.135; standard deviation, 0.220). Intraocular pressure remained stable in all treatment groups. Other safety parameters did not raise any concerns.

Discussion

The results of the double-masked, phase 3 VEKTIS trial demonstrated the efficacy and safety of CsA CE in this study cohort of children and adolescents with severe VKC. The study achieved its primary end point, demonstrating the superiority of CsA CE high-dose and CsA CE low-dose treatment over vehicle on the composite efficacy score during the 4-month treatment period ($P = 0.007$ and $P = 0.010$, respectively). The benefit of CsA CE treatment was driven largely by a decrease in the CFS score (reflecting less corneal damage), and to a lesser extent, by a decrease in rescue dexamethasone use. The secondary efficacy end points supported the superiority of CsA CE over vehicle,

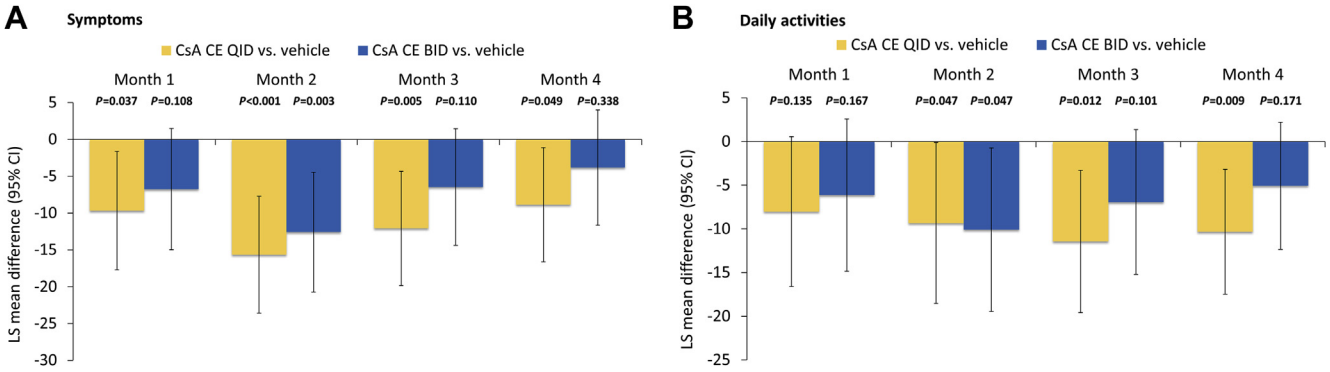

Figure 5. Graphs showing improvement in quality of life (QoL) on the Quality of Life in Children with Vernal Keratoconjunctivitis questionnaire (**A**) symptoms domain and (**B**) daily activities domain. Minimum QoL score is defined as 0 (positive) and maximum is 100 (negative). *P* values were derived via linear mixed model for repeated measures with adjustment through the Hochberg's procedure. BID = twice daily; CI = confidence interval; CsA CE = cyclosporine A cationic emulsion 0.1% (1 mg/ml); LS = least-squares; QID = 4 times daily.

particularly in the high-dose group, in which significant improvements in key VKC symptoms, QoL, and responder rate were evident. Thus, the efficacy of CsA CE in VKC was supported by both objective and subjective improvement.

The greatest improvement in the composite efficacy score was achieved from baseline to month 1, indicating that treatment benefits occurred rapidly. Thereafter, improvements in the CsA CE groups paralleled the improvement noted in the vehicle group, demonstrating that the initial treatment benefit was maintained throughout the 4-month treatment period. Previous VKC studies with other CsA formulations and higher CsA concentrations also showed rapid improvement and sustained benefit with continued treatment, with one study indicating that CsA's beneficial effects were independent of any underlying atopic condition.[14,25] However, the VEKTIS study is the first to enroll a large number of patients with severe VKC and to demonstrate efficacy with respect to measures of VKC signs, symptoms, and QoL; limiting disease progression; and reducing the use of rescue medication (corticosteroids).

The incidence of corneal ulcers was low in our study, which can be attributed to the anti-inflammatory effects of CsA (e.g., reduction of hyperemia and CFS score), as well as the use of rescue medication in the event of disease worsening; in addition, the CE vehicle itself has been shown to have beneficial aspects on keratitis, which may explain the lack of a significant difference between the CsA CE and vehicle groups with respect to ulcer formation. Improvements seen in the vehicle group—not only in terms of ulceration, but other VKC measures as well—likely reflect a beneficial lubricating effect consistent with the known symptomatic benefits of artificial tears in VKC,[4,10] as well as changes in VKC severity during the allergy season. The CsA CE formulation used herein was formulated specifically to enhance CsA bioavailability in the eye and was associated with negligible systemic CsA exposure. Consistent with this negligible exposure, there were no clinically relevant changes in alanine aminotransferase, aspartate aminotransferase, or creatinine over the 4-month treatment period.

The safety data were consistent with the known safety profile of topically applied CsA, and no unexpected safety findings were identified. The incidences and types of treatment-related TEAEs generally were similar across treatment groups, although instillation site pain was reported slightly more often in the high-dose CsA CE group versus the other groups. Most TEAEs were mild or moderate in severity and rarely led to discontinuation of CsA CE treatment.

One limitation of our study was that we enrolled only patients with severe VKC because it was considered more appropriate to evaluate CsA CE in this population, rather than in patients with less severe disease, for whom other treatment options were available. In future studies, it may be of interest to assess the efficacy of CsA CE in patients with moderate VKC as well. A second limitation was the 4-month comparative period for evaluation of the efficacy of CsA CE. We chose this timeframe to ensure that all patients were assessed during the allergy season; however, depending on the country and the year, the allergy season can be longer than 4 months, so it is possible that some patients were not evaluated for the entire season. Nevertheless, we observed progressive and statistically significant improvements in the primary end point and in VKC signs and symptoms during the treatment period. A third limitation was that the modified Oxford scoring system used to assess CFS data was developed for use in patients with dry eye disease, rather than VKC. Although this system is validated for the grading of ocular surface disease, the pattern of corneal and conjunctival staining in dry eye disease is not the same as with VKC, in which there is a predominance of staining on the superior half of the cornea with mucus adhesion. A new, VKC-specific scoring system (VKC-Collaborative Longitudinal Evaluation of Keratoconus) was introduced recently in an effort to address some of these limitations,[26] but it was not available at the time our study design was being finalized. And finally, the VEKTIS study lacked a true placebo comparator. In ocular allergy trials, there can be no true placebo because any topical product has an effect, even if it is a modest one; tear substitutes, for example, act as an eyewash, diluting the concentration of the allergens and mediators in tears.[4] In addition, it is not ethically acceptable to have children with severe VKC receiving placebo in a clinical trial.

Table 3. Summary of Treatment-Emergent Adverse Events and Treatment-Related Treatment-Emergent Adverse Events during the 4-Month Treatment Period

Parameter	Cyclosporine A Cationic Emulsion 0.1% (1 mg/ml) 4 Times Daily (n = 57)	Cyclosporine A Cationic Emulsion 0.1% (1 mg/ml) Twice Daily (n = 54)	Vehicle (n = 58)
TEAEs*			
Patients with ≥1 TEAEs	24 (42.1)	18 (33.3)	23 (39.7)
Patients with serious TEAEs	2 (3.5)	1 (1.9)	0 (0)
Discontinuations because of TEAEs	1 (1.8)	0 (0)	2 (3.4)
Most common TEAEs*			
Eye disorders			
Ulcerative keratitis	4 (7.0)	3 (5.6)	3 (5.2)
Corneal leukoma	2 (3.5)	0 (0)	1 (1.7)
Foreign body sensation in eyes	2 (3.5)	0 (0)	0 (0)
Other TEAEs			
Instillation site pain	6 (10.5)	3 (5.6)	2 (3.4)
Instillation site pruritus	2 (3.5)	2 (3.7)	2 (3.4)
Headache	4 (7.0)	0 (0)	1 (1.7)
Instillation site erythema	1 (1.8)	1 (1.9)	2 (3.4)
Nasopharyngitis	0 (0)	3 (5.6)	1 (1.7)
Pharyngitis	2 (3.5)	0 (0)	0 (0)
Cough	2 (3.5)	0 (0)	0 (0)
Pyrexia	0 (0)	1 (1.9)	2 (3.4)
Treatment-related TEAEs			
Patients with treatment-related TEAEs	11 (19.3)	5 (9.3)	9 (15.5)
Patients with serious treatment-related TEAEs	0 (0)	0 (0)	0 (0)
Discontinuations because of treatment-related TEAEs	1 (1.8)	0 (0)	2 (3.4)
Eye disorders			
Eye irritation	1 (1.8)	0 (0)	0 (0)
Eye pain	1 (1.8)	0 (0)	0 (0)
Ocular hyperemia	1 (1.8)	0 (0)	0 (0)
Blepharospasm	1 (1.8)	0 (0)	0 (0)
Eyelid erosion	1 (1.8)	0 (0)	0 (0)
Corneal leukoma	0 (0)	0 (0)	1 (1.7)
Cataract, subcapsular	0 (0)	0 (0)	1 (1.7)
Eyelid edema	0 (0)	0 (0)	1 (1.7)
Visual acuity reduced	0 (0)	0 (0)	1 (1.7)
Other treatment-related TEAEs			
Instillation site pain	6 (10.5)	3 (5.6)	2 (3.4)
Instillation site pruritus	1 (1.8)	2 (3.7)	2 (3.4)
Instillation site erythema	0 (0)	1 (1.9)	2 (3.4)
Rhinorrhea	1 (1.8)	0 (0)	0 (0)
Headache	1 (1.8)	0 (0)	0 (0)
Application site swelling	0 (0)	1 (1.9)	0 (0)
Application site discharge	0 (0)	0 (0)	1 (1.7)
Throat tightness	0 (0)	0 (0)	1 (1.7)
Rash	0 (0)	0 (0)	1 (1.7)
Intraocular pressure increased	0 (0)	0 (0)	1 (1.7)

TEAE = treatment-emergent adverse events.
Data are no. (%).
*Treatment-emergent adverse events occurring in 2 or more patients in any group.

In conclusion, pediatric patients treated with CsA CE achieved significant improvements in the signs and symptoms of severe VKC compared with patients who received vehicle alone, with high-dose CsA CE showing more numerous conclusive statistical results versus vehicle than the low-dose group, much larger improvements in photophobia and mucous discharge, and much larger improvements for both QoL domains. Both doses of CsA CE demonstrated favorable safety profiles, which were similar between groups, with the exception of 1 treatment-related event—instillation site pain—which occurred more frequently in the high-dose group. The effects of continued treatment with CsA CE are being assessed in an 8-month safety follow-up period and will be reported in a subsequent publication.

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References

1. Brémond-Gignac D, Donadieu J, Leonardi A, et al. Prevalence of vernal keratoconjunctivitis: a rare disease? *Br J Ophthalmol*. 2008;92:1097–1102.
2. Hayilu D, Legesse K, Lakachew N, Asferaw M. Prevalence and associated factors of vernal keratoconjunctivitis among children in Gondar City, Northwest Ethiopia. *BMC Ophthalmol*. 2016;16:167.
3. Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res*. 2002;21:319–339.
4. Leonardi A. Management of vernal keratoconjunctivitis. *Ophthalmol Ther*. 2013;2:73–88.
5. Aragona P, Romeo GF, Puzzolo D, et al. Impression cytology of the conjunctival epithelium in patients with vernal conjunctivitis. *Eye (Lond)*. 1996;10:82–85.
6. Vichyanond P, Pacharn P, Pleyer U, Leonardi A. Vernal keratoconjunctivitis: a severe allergic eye disease with remodeling changes. *Pediatr Allergy Immunol*. 2014;25:314–322.
7. Tabbara KF. Ocular complications of vernal keratoconjunctivitis. *Can J Ophthalmol*. 1999;34:88–92.
8. Sacchetti M, Baiardini I, Lambiase A, et al. Development and testing of the quality of life in children with vernal keratoconjunctivitis questionnaire. *Am J Ophthalmol*. 2007;144:557–563.e2.
9. Bonini S, Lambiase A, Sgrulletta R, Bonini S. Allergic chronic inflammation of the ocular surface in vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol*. 2003;3:381–387.
10. Kumar S. Vernal keratoconjunctivitis: a major review. *Acta Ophthalmol*. 2009;87:133–147.
11. Gokhale NS. Systematic approach to managing vernal keratoconjunctivitis in clinical practice: severity grading system and a treatment algorithm. *Indian J Ophthalmol*. 2016;64:145–148.
12. BenEzra D, Peter J, Brodsky M, Cohen E. Cyclosporine eyedrops for the treatment of severe vernal keratoconjunctivitis. *Am J Ophthalmol*. 1986;101:278–282.
13. Lambiase A, Leonardi A, Sacchetti M, et al. Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study. *J Allergy Clin Immunol*. 2011;128:896–897.e9.
14. Pucci N, Novembre E, Cianferoni A, et al. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol*. 2002;89:298–303.
15. Pucci N, Caputo R, Mori F, et al. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. *Int J Immunopathol Pharmacol*. 2010;23:865–871.
16. Secchi AG, Tognon MS, Leonardi A. Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. *Am J Ophthalmol*. 1990;110:641–645.
17. Lallemand F, Felt-Baeyens O, Besseghir K, et al. Cyclosporine A delivery to the eye: a pharmaceutical challenge. *Eur J Pharm Biopharm*. 2003;56:307–318.
18. Lallemand F, Daull P, Benita S, et al. Successfully improving ocular drug delivery using the cationic nanoemulsion, novasorb. *J Drug Deliv*. 2012;2012:604204.
19. Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. *Prog Retin Eye Res*. 2002;21:15–34.
20. Baudouin C, de la Maza MS, Amrane M, et al. One-year efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease. *Eur J Ophthalmol*. 2017;27:678–685.
21. Baudouin C, Figueiredo FC, Messmer EM, et al. A randomized study of the efficacy and safety of 0.1% cyclosporine A cationic emulsion in treatment of moderate to severe dry eye. *Eur J Ophthalmol*. 2017;27:520–530.
22. Leonardi A, Van Setten G, Amrane M, et al. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial. *Eur J Ophthalmol*. 2016;26:287–296.
23. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*. 2003;22:640–650.
24. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol*. 2007;7:436–441.
25. Kiliç A, Gürler B. Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol*. 2006;41:693–698.
26. Leonardi A, Lazzarini D, La Gloria Valerio A, et al. Corneal staining patterns in vernal keratoconjunctivitis: the new VKC-CLEK scoring scale. *Br J Ophthalmol*. 2018;102:1448–1453.

Footnotes and Financial Disclosures

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A complete listing of the VEKTIS study investigators is available at www.aaojournal.org.

HUMAN SUBJECTS: Human subjects were included in this study. The study was conducted in accordance with ethical principles originating in the Declaration of Helsinki and in compliance with International Conference on Harmonisation guidelines of Good Clinical Practice and applicable local ethical and legal requirements. Independent ethics committees and regulatory agencies approved the study protocol prior to study initiation (see Appendix [available at www.aaojournal.org] for further details). The parents or legal guardian of each patient provided written informed consent, and the patient provided assent when possible.

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Abbreviations and Acronyms:
BID = twice daily; **CFS** = corneal fluorescein staining; **CI** = confidence interval; **CsA CE** = cyclosporine A cationic emulsion; **FAS** = full analysis set; **IGEE** = investigator global evaluation of efficacy; **LS** = least-squares; **QID** = 4 times daily; **QoL** = quality of life; **SEM** = standard error of the mean; **TEAE** = treatment-emergent adverse event; **VAS** = visual analog scale; **VEKTIS** = VErnal KeratoconjunctiviTIs Study; **VKC** = vernal keratoconjunctivitis.

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