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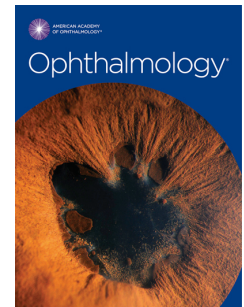
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A Randomized, Controlled Trial of Cyclosporine A Cationic Emulsion in Pediatric Vernal Keratoconjunctivitis: The VEKTIS Study

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RUNNING HEAD

VEKTIS: cyclosporine A (CsA) cationic emulsion in pediatric VKC

This article contains additional online-only material. The following should appear online only: Appendix.

ABSTRACT

Background: 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.

Purpose: This study evaluated the efficacy and safety of an investigational therapy for severe VKC, cyclosporine A cationic emulsion (CsA CE), an oil-in-water emulsion with increased bioavailability versus conventional CsA formulations.

Design: VEKTIS is a phase 3, multicenter, double-masked, vehicle-controlled trial.

Participants: Pediatric patients (4-18 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: 169 patients were randomized to CsA CE 0.1% (1 mg/mL) eye drops four times daily (QID, high-dose), CsA CE twice daily (BID, low-dose) + vehicle BID, or vehicle QID for 4 months.

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

Results: Differences in least-squares means versus vehicle for the primary endpoint were statistically significant for both the high-dose (0.76, $P=0.007$) and the low-dose group (0.67, $P=0.010$), with treatment effect mainly driven by CFS score. Significant differences were found between both active treatment groups and vehicle for use of rescue medication. VKC symptoms and patient QoL (assessed by visual analogue scale and the Quality of Life in Children with Vernal Keratoconjunctivitis [QUICK]

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.

KEY WORDS

Cationic emulsion; Corneal fluorescein staining; Cyclosporine A; Inflammation; Keratitis; Quality of life; QUICK questionnaire; Randomized controlled trial; Vernal keratoconjunctivitis

ABBREVIATIONS AND ACRONYMS**AE**, adverse event**ANCOVA**, analysis of covariance**ALT**, alanine aminotransferase**AST**, aspartate aminotransferase**BCDVA**, best corrected distance visual acuity**BID**, twice daily**CE**, cationic emulsion**CFS**, corneal fluorescein staining**CI**, confidence interval**CsA**, cyclosporine A**CsA CE**, cyclosporine A cationic emulsion**FAS**, full analysis set**IGEE**, investigator global evaluation of efficacy**IOP**, intraocular pressure**LMMRM**, linear mixed model for repeated measures**LS**, least-squares**QID**, four times daily**QoL**, quality of life**QUICK**, Quality of Life in Children with Vernal Keratoconjunctivitis**SEM**, standard error of the mean**TEAE**, treatment-emergent adverse event**VAS**, visual analogue scale

111 **VKC**, vernal keratoconjunctivitis

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 VKC is an orphan disease, with prevalence estimated at 3.2/10,000 inhabitants (0.03%) in the European Union.¹

VKC is characterized by allergic inflammation of the ocular surface, with clinical manifestations involving the tarsal (palpebral) and/or bulbar conjunctiva, which can have a seasonal course but may also 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 may in turn result in corneal scarring, thinning, and visual loss.⁷ Corneal complications/keratitis are estimated to occur in 25-50% of cases.¹

VKC typically occurs in school-age children, with an age of onset prior to 10 years in 80% of cases (typical range, 4–7 years), and is reported in males 3 to 4 times more often than in females.^{1,6} VKC often resolves after puberty, although it may persist in adulthood, where the male:female ratio is closer to 1:1.^{4,6} Children with severe VKC

may have a poor quality of life (QoL) due to limitations in daily activities/
schooling/vacationing, as well as potential psychological/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 pharmacological 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 non-steroidal 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 are often necessary in moderate-to-severe disease; though effective,
they must be used for short courses due to 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 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 0.1% (1 mg/mL) (CsA CE) 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 CsA CE was also shown to provide a significant reduction of VKC signs during a 4-week treatment period, particularly in patients with severe keratitis (Data on File, Santen). 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, to February 1, 2016, at 51 sites in 11 countries (Spain, France, India, Italy, Israel, United States, Greece, Hungary, Portugal, Croatia, Germany).

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 (as appropriate) approved the study protocol prior to study initiation. The parents or legal guardian of each patient provided written informed consent, and the patient provided assent when possible. The study was prospectively registered with ClinicalTrials.gov (NCT01751126).

The study included a 4-month efficacy/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 randomly assigned in a 1:1:1 ratio to receive 1 drop of CsA CE 0.1% (1 mg/mL) four times daily (QID; high-dose), 1 drop of CsA CE two times daily (BID; low-dose) plus 1 drop of vehicle BID, or 1 drop of vehicle QID. Treatment assignments were generated using a computerized randomization schema, stratified by country, and centralized using an interactive web-response system.

Patients/caregivers were educated regarding the optimal technique for ophthalmic drop instillation and 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% QID for up to 5 days) was permitted in the event of keratitis (corneal fluorescein staining [CFS] score based on modified Oxford scale²³ (7-point scale; range, 0-5 [absence of staining to greatest severity]; individual grades: 0, 0.5, 1, 2, 3, 4, 5) worsening by ≥ 1 grade or maintenance of the CFS score for 2 months at the entry level, and/or symptom worsening of ≥ 10 mm for ≥ 1 of the 4 VKC symptoms plus worsening or maintenance at the entry level of the mean visual analogue scale (VAS) score for the 4 symptoms. Dexamethasone had to be given at least 30 minutes before or after study medication. A maximum of 2 courses was allowed between study visits.

PATIENTS

Eligible patients included males or females aged 4 to <18 years with active severe VKC (grade 3 or 4 on the Bonini scale²⁴) and severe keratitis with a CFS score of grade 4 or 5 on the modified Oxford scale. Patients were required to have experienced ≥ 1 recurrence 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 on a 0–100 mm VAS (0, no symptoms; 100, comparable to the worst discomfort ever experienced). Enrollment had to occur early during the allergy season for that site in order to allow the 4-month treatment period to occur during the VKC season.

Subjects were excluded if they had ocular anomalies other than VKC affecting the ocular surface; abnormalities of lid anatomy, 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 was also an exclusion criterion. Subjects were not tested with a skin prick test or required to have a specific IgE blood level as part of the inclusion criteria. Topical or systemic corticosteroids within 1 week, topical CsA, tacrolimus, or sirolimus or any systemic immunosuppressive drug within 90 days prior to enrollment, or 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 on 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 shown below:

- 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 endpoint was defined as the mean of the composite scores recorded at the 4 monthly visits.

Secondary efficacy endpoints 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 [QUICK] 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 QUICK 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 $\leq 50\%$ of the Baseline value, and he/she did not withdraw for a reason possibly due to treatment, did not experience ulceration, and did not use rescue medication during the last 3 months of treatment.

Other parameters assessed were conjunctival erythema/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/hyperemia, conjunctival discharge, conjunctival chemosis, papillae, and limbal infiltrates were constructed as follows: For conjunctival erythema/hyperemia, conjunctival discharge, and conjunctival chemosis, 0=Absent; 1=Mild; 2=Moderate; 3=Severe; for papillae, 0=Absent; 1=Mild hyperemic scattered papillae; 2=Moderate diffuse hyperemic swollen papillae; 3=As before but more severe; 4=Hyperemic swollen giant papillae covering the superior tarsal plate; for limbal infiltrates, 0=Absent; 1=Mild limbus hyperemia and swelling; 2=Moderate limbus hyperemia and swelling; 3=As before but more severe; 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 (AEs) were monitored throughout the study. Best-corrected distance visual acuity (BCDVA) and intraocular pressure (IOP) by tonometry were assessed at each visit. Blood samples for measurement of CsA levels, serum creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were collected at Baseline and Months 2 and 4.

STATISTICAL ANALYSIS

Efficacy parameters were evaluated in the full analysis set (FAS), which consisted of all randomized patients who received ≥ 1 dose of study medication, and who did not have early withdrawal during the first week for reasons definitely unrelated to study medication (thus resulting in a lack of post-randomization data). For the primary endpoint, the superiority of CsA CE over vehicle was evaluated using an analysis of covariance (ANCOVA) 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 AE (4.1%). Notably, more patients in the CsA CE low-dose and vehicle groups versus the CsA CE high-dose group withdrew early due to lack of efficacy (9.3%, 8.6%, versus 1.8%, respectively). One randomized patient did not have severe active VKC at Baseline and was therefore excluded from the FAS.

The demographic and Baseline clinical characteristics of the 3 treatment groups were generally well balanced (**Table 1**). Overall, the mean age was 9.2 years; 78.6% of patients were male; and 70.8% were Caucasian. The mean time since VKC diagnosis was 3.4 years. Most patients (65.5%) had the mixed form of VKC (both limbal and tarsal signs), with perennial VKC diagnosed in 55.4%. The majority had VKC grade 3 (61.9%) and a CFS score of 4 (86.3%) at Baseline (13.7% had a CFS score of 5). Notably, more patients in the CsA CE high-dose group had 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 ENDPOINT)

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 endpoint) was 2.06 (95% 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 endpoint, 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 course of rescue medication over the 4 months was 32.1%, 31.5%, and 53.4% in the QID, BID, and vehicle groups, and the mean number of rescue courses was 0.66, 0.69, and 1.31, respectively ($P=0.010$, high-dose group versus vehicle; $P=0.055$, low-dose versus vehicle). There was no difference in the mean number of ulcer occurrences per month across treatment groups (0.001 for QID, 0.003 for BID; $P=0.996$ for both versus 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 were generally favored over vehicle in terms of the composite efficacy scores across most subgroups defined by patient Baseline characteristics (**Fig 3**).

OTHER EFFICACY ENDPOINTS

The benefits of CsA CE treatment, particularly with the high dose, were evident on most secondary efficacy endpoints. 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. CsA CE high-dose provided significantly greater symptom improvement versus vehicle at Months 1, 2, and 4 for photophobia, Months 2 and 4 for tearing, and at all monthly time points for itching and mucous discharge (**Fig 4**). Significant improvements with CsA CE low-dose versus vehicle were primarily noted 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. QoL, as measured by the Symptoms and Daily Activities domain scores on the QUICK 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 (7.4%) in the low-dose group, and 1 (1.7%) of those receiving vehicle alone

had 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/hyperemia, conjunctival discharge, papillae, limbal infiltrates, and conjunctival chemosis in all treatment groups. The assessment of conjunctival erythema/hyperemia showed a statistically significant difference between the active treatments versus vehicle ($P=0.017$ and $P=0.031$, respectively); the proportion with grade 2-3 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

The majority of 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 had serious adverse events (severe 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 ALT, AST, 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.

BCDVA 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]). IOP 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 endpoint, demonstrating the superiority of CsA

CE high-dose and CsA CE low-dose 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 usage. The secondary efficacy endpoints supported the superiority of CsA CE over vehicle, particularly in the high-dose group, where 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 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 (eg, 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 term 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 specifically formulated 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 ALT, AST, 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 were generally 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 only enrolled patients with severe VKC, as 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 endpoint 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, where 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 [VKC-CLEK]) was recently introduced 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, it should be noted, there can be no true placebo because any topical product has an effect, even if it is a modest one; tear substitutes, eg, 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 on placebo in a clinical trial.

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, 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 one 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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The authors thank the VEKTIS investigators for the inclusion of their patients in the study. A full list of the investigators can be found in the Appendix (available at www.aaojournal.org). The authors also thank Barry Weichman, PhD for medical writing support and BioScience Communications, New York, NY, USA, for medical writing and copyediting support (all funded by Santen SAS) and Maëva Deniaud (MD, Statistical Consulting) and Prof. Bruno Scherrer for statistical and methodology advice.

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FIGURE LEGENDS

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

Figure 2. (A) Mean composite efficacy score at each visit; (B) 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 (CFS) 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, four times daily.

Figure 3. Forest plot of (A) high-dose CsA CE (QID) and (B) low-dose CsA CE (BID) versus vehicle alone for the composite efficacy score in key subgroups. 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. BID, twice

daily; CFS, corneal fluorescein staining; CI, confidence interval; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); LS, least-squares; QID, four times daily; VAS, visual analogue scale; VKC, vernal keratoconjunctivitis.

Figure 4. Improvement on the VAS (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 LMMRM 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; LMMRM, linear mixed model for repeated measures; QID, four times daily; SEM, standard error of the mean; VAS, visual analogue scale.

Figure 5. Improvement in quality of life (QoL) on the QUICK 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 LMMRM with adjustment through the Hochberg's procedure. BID, twice daily; CI, confidence interval; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); LMMRM, linear mixed model for repeated measures; LS, least-squares; QID, four times daily; QUICK, Quality of Life in Children with Vernal Keratoconjunctivitis.

Table 1. Demographic and Baseline Characteristics of the FAS Cohort

Characteristic	CsA CE QID (N=56)	CsA CE BID (N=54)	Vehicle (N=58)
Age, years: mean (SD)	9.1 (3.3)	9.6 (3.4)	8.9 (3.2)
Age group, n (%)			
Age 4–11 years	43 (76.8)	38 (70.4)	46 (79.3)
Age 12–18 years	13 (23.2)	16 (29.6)	12 (20.7)
Sex, n (%)			
Male	44 (78.6)	42 (77.8)	46 (79.3)
Female	12 (21.4)	12 (22.2)	12 (20.7)
Race, n (%)			
Caucasian	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, n (%)			
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, n (%)			
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, ^a n (%)			
Grade 3	32 (57.1)	32 (59.3)	40 (69.0)
Grade 4	24 (42.9)	22 (40.7)	18 (31.0)
CFS score, ^a n (%)			
Grade 4	42 (75.0)	49 (90.7)	54 (93.1)
Grade 5	14 (25.0)	5 (9.3)	4 (6.9)
Asthma, n (%)	12 (21.4)	10 (18.5)	11 (19.0)

^aGrade or score of analysis eye; VKC grading by Bonini scale and CFS score by modified Oxford scale. BID, twice daily; CFS, corneal fluorescein staining; CsA CE, cyclosporine A cationic

emulsion 0.1% (1 mg/mL); FAS, full analysis set; QID, four times daily; SD, standard deviation; VKC, vernal keratoconjunctivitis.

Table 2. Analysis of Composite Primary Endpoint and its Components

Endpoint	CsA CE high-dose vs. vehicle	CsA CE low-dose vs. vehicle
Composite efficacy score (primary endpoint)^a		
LS mean (95% CI)	0.76 (0.26, 1.27)	0.67 (0.16, 1.18)
Adjusted P-value ^b	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 ^b	0.014	0.014
Relative contribution to primary endpoint	70.3%	77.6%
Mean number 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 ^b	0.010	0.055
Relative contribution to primary endpoint	29.6%	21.9%
Mean number of ulcer occurrences per month		
LS mean (95% CI)	0.001 (−0.04, 0.04)	0.003 (−0.03, 0.04)
Adjusted P-value ^b	0.966	0.966
Relative contribution to primary endpoint	0.1%	0.5%

^aThe composite score at each monthly visit was calculated as the difference in corneal fluorescein staining (CFS) score from Baseline, with penalties of −1 for each course of rescue medication or occurrence of corneal ulceration; a positive value indicated improvement;

^bANCOVA model with adjustment through the Hochberg's procedure. ANCOVA, analysis of covariance; CFS, corneal fluorescein staining; CI, confidence interval; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); LS, least-squares; vs., versus.

Table 3. Summary of Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs During 4-Month Treatment Period

Parameter, n (%)	CsA CE QID (N=57)	CsA CE BID (N=54)	Vehicle (N=58)
TEAEs^a			
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 due to TEAEs	1 (1.8)	0 (0)	2 (3.4)
Most common TEAEs^a			
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 due to 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)

^aTEAEs occurring in ≥ 2 patients in any group. BID, twice daily; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); QID, four times daily.

Fig. 1

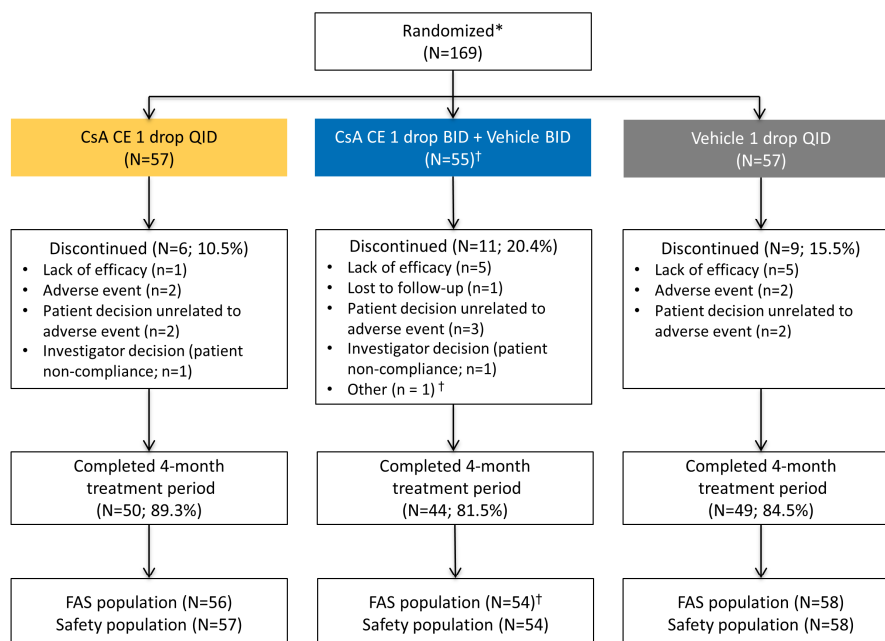


Fig. 2A

A.

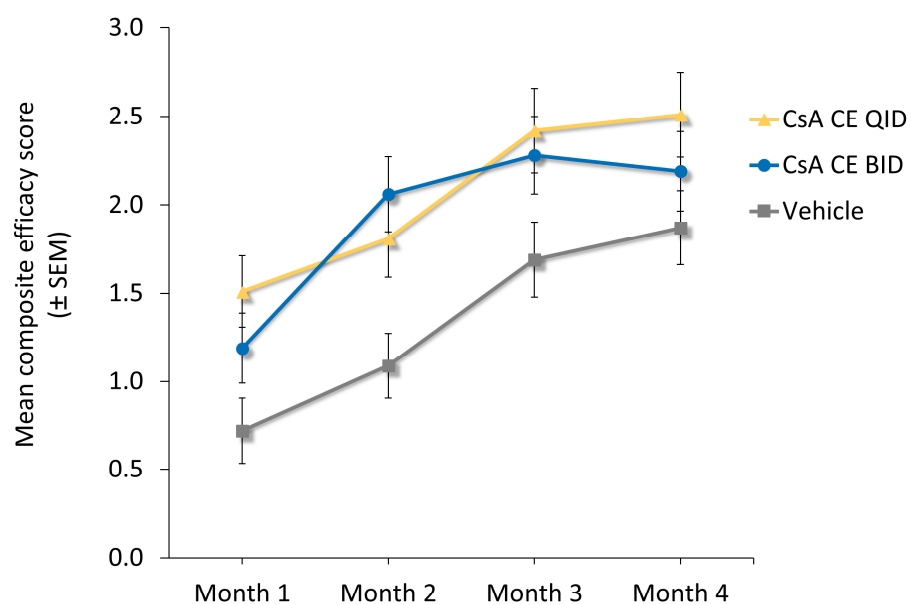


Fig. 2B

B.

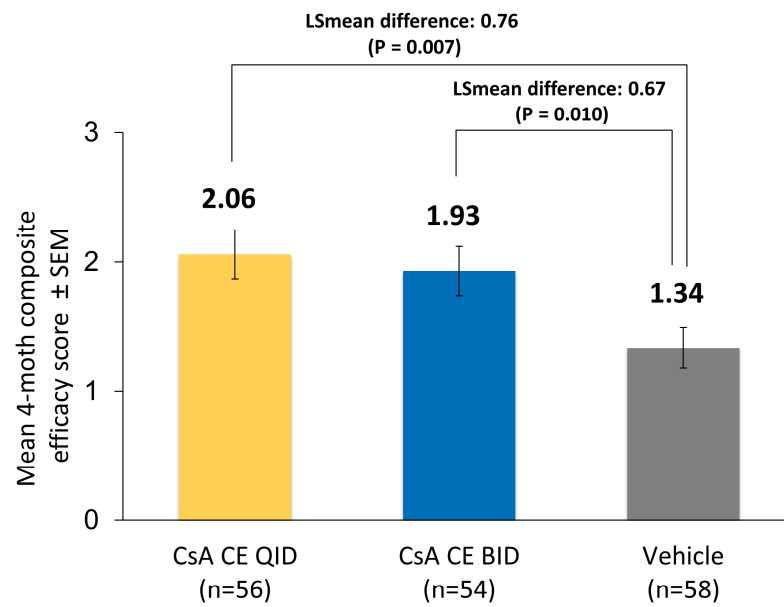


Fig. 3A

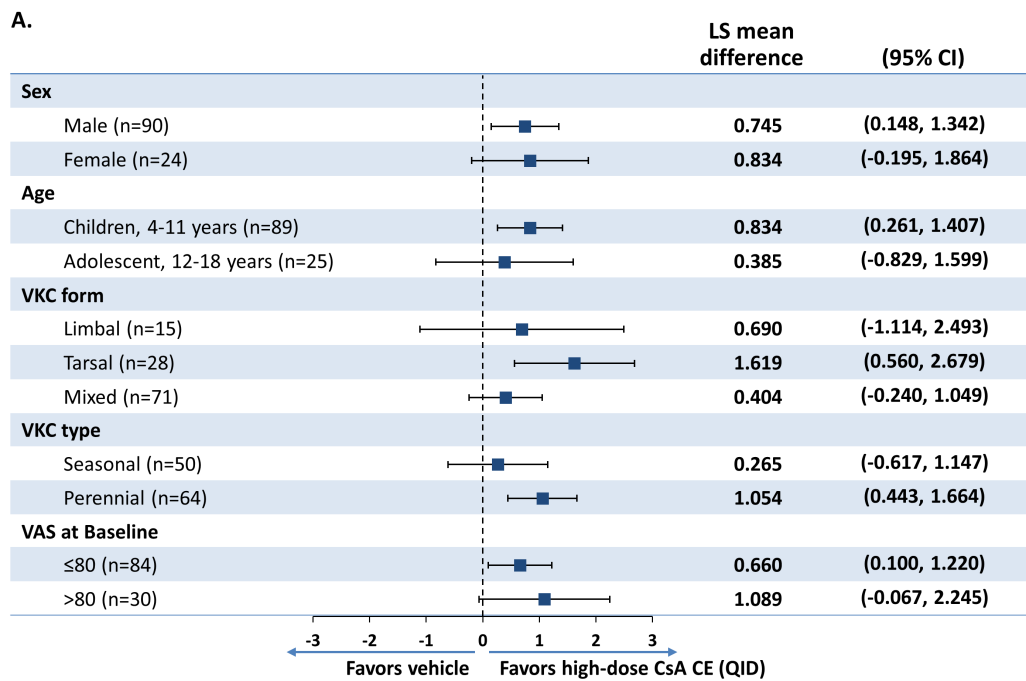


Fig. 3B

B.

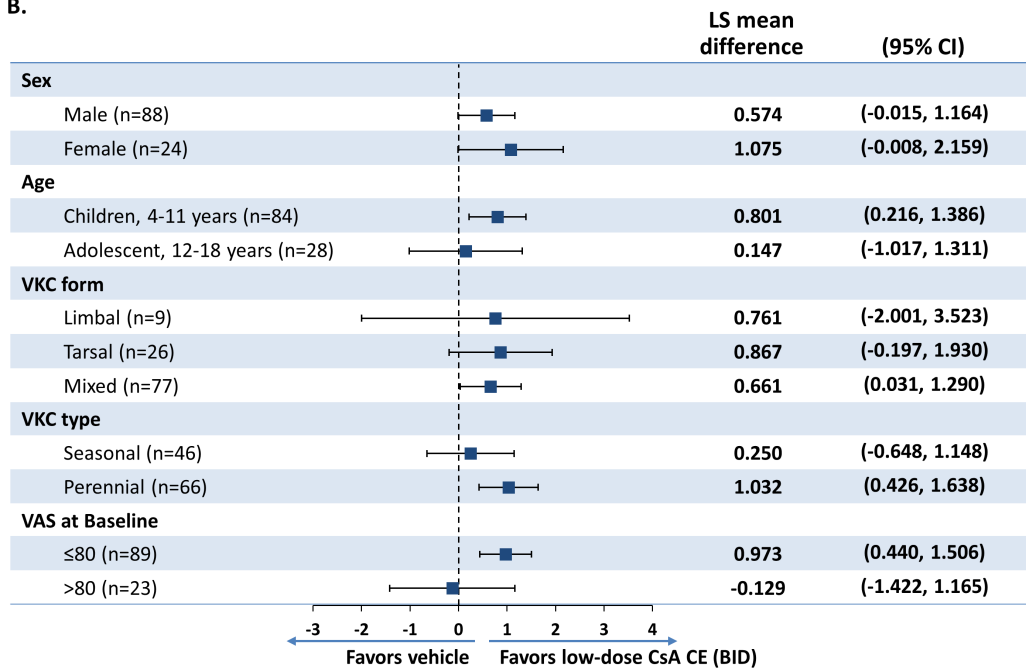


Fig. 4A

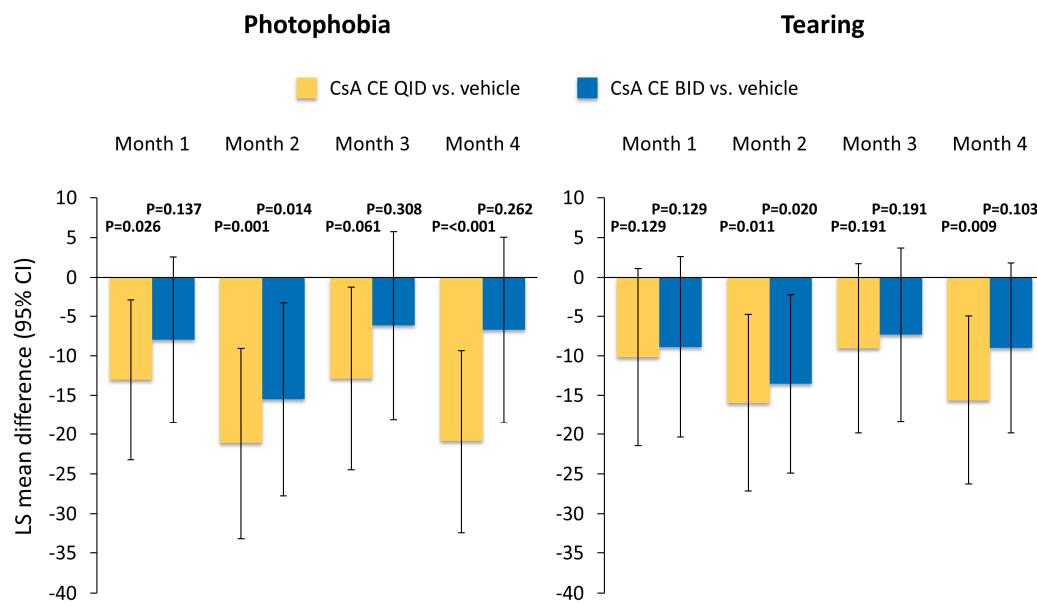


Fig. 4B

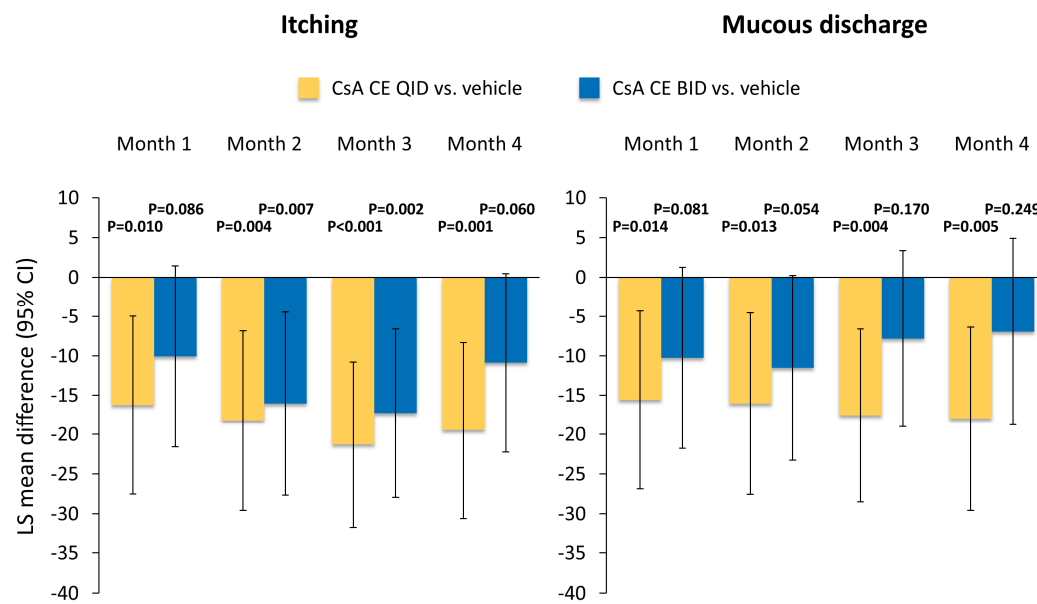


Fig. 5A

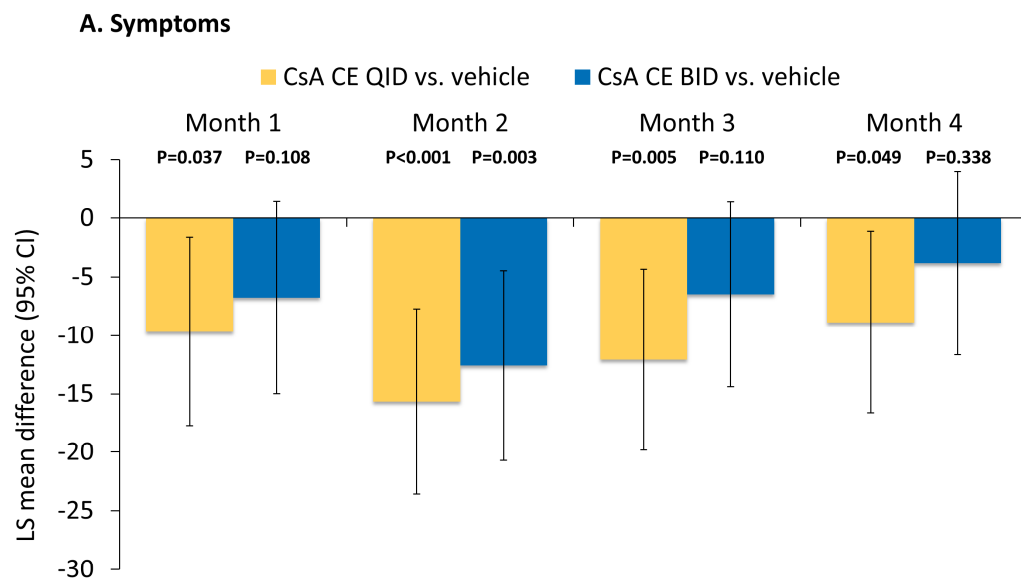
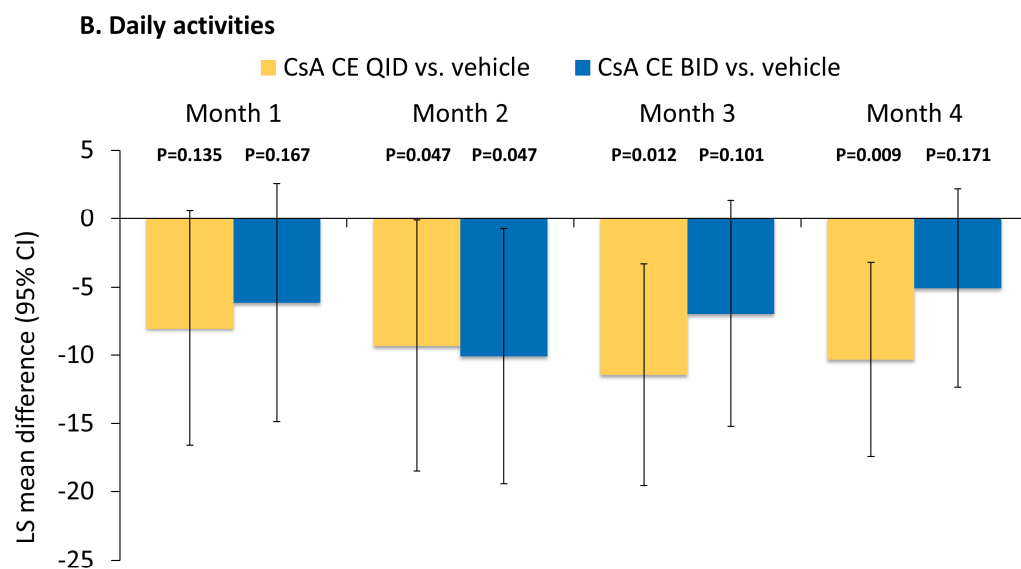


Fig. 5B



Appendix

A Randomized, Controlled Trial of Cyclosporine A Cationic Emulsion in Pediatric Vernal Keratoconjunctivitis: The VEKTIS Study

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METHODS

Safety

Ocular parameters included anterior chamber inflammation and lens opacification, each graded on a numerical scale (0-3). Numerical scales for these parameters were constructed as follows: For anterior chamber inflammation, 0=None (no Tyndall effect); 1=Mild (Tyndall effect barely discernible); 2=Moderate (Tyndall beam in the anterior chamber is moderately intense); 3=Severe (Tyndall beam in the anterior chamber is severely intense); and for lens opacification, 0=No opacification (normal lens); 1=Mild lens opacification; 2=Moderate lens opacification; 3=Severe lens opacification.

Statistical Analyses

Sample size calculation. According to the results of a prior study performed in patients with vernal keratoconjunctivitis (VKC), it was noted that results at 1 month (the duration of the double-masked period) showed an improvement in corneal fluorescein staining (CFS) score of 1.5 grades (based on the modified Oxford scale) in the active group versus the vehicle group. For the current study, it seemed reasonable to expect a slightly lower difference, but one that would be maintained over the 4-month treatment period during which efficacy evaluations would be performed (1.25 grades of difference in the mean of the 4 assessments for the active groups vs. vehicle).

Based on this assumption and a standard deviation of 2 that was observed in the previous study, and setting the two-sided alpha risk at 2.5% to take into account a multiplicity adjustment for the two tested dose regimens, a sample size of 50 patients per group was estimated to be required to yield an 80% chance (power) to achieve a significant difference between the most efficacious dose and vehicle. A provision of 12% was arbitrarily added to the sample size (56 patients per group) for the decrease of power linked to an early end of VKC season in some regions and possible early withdrawals.

The worst eye at study entry was considered in the primary analysis. Type I error was adjusted through the Hochberg procedure for comparing each dose to placebo. The ANCOVA (analysis of covariance) model was also applied separately to analyze each component of the primary efficacy endpoint. The relative contribution of each component to the overall treatment effect was calculated from the least-squares (LS) mean ratio for the component to the overall effect.

Changes in efficacy parameters over time were evaluated using a linear mixed model for repeated measures (LMMRM), with treatment, visit, exposure to VKC season, treatment-by-visit interaction, and patient as covariates. A p-value ≤ 0.10 was indicative of a significant change over time. The responder rate was evaluated by logistic regression using treatment and exposure to VKC season as covariates. The IGEE was evaluated using a proportional odds model with treatment and exposure to VKC season as covariates. The proportion of patients with a positive

assessment (modalities 2 or 3; satisfactory or very satisfactory) was pooled and compared with the proportion with a negative assessment (modalities 0 or 1; unsatisfactory or not very satisfactory) using Fisher's exact test.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and evaluated descriptively. Local ocular tolerance parameters and other safety parameters were also evaluated descriptively.

Précis

Cyclosporine A cationic emulsion improved multiple manifestations of severe vernal keratoconjunctivitis in a Phase 3 study conducted in a pediatric population, suggesting therapeutic potential in this sometimes sight-threatening orphan condition, currently managed using off-label treatments.