Twelve-Month Results of Cyclosporine A Cationic Emulsion in a Randomized Study in Patients With Pediatric Vernal Keratoconjunctivitis

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• PURPOSE: To assess the safety and efficacy of cyclosporine A cationic emulsion (CsA CE) 0.1% eye drops in pediatric patients with severe active vernal keratoconjunctivitis (VKC).

• DESIGN: Multicenter, double-masked, randomized controlled trial 8-month safety analysis.

• METHODS: Of 169 patients (age range, 4-17 years) initially randomized in the 4-month VErnal KeratoconjunctiviTIs Study (VEKTIS), 142 entered the 8-month follow-up period during which CsA CE patients remained on their original regimen (CsA CE 4 times daily [QID, high-dose] or CsA CE twice daily [BID, low-dose] + vehicle BID) and vehicle patients were allocated to one of these 2 active regimens. Main outcome measures were safety, including treatment-emergent adverse events, and efficacy, including corneal fluorescein staining (CFS) score.

• RESULTS: Improvements in CFS score, rescue medication use, key VKC symptoms (photophobia, tearing, itching, and mucous discharge), and quality of life (QoL) assessed by QUICK questionnaire observed with CsA CE compared with vehicle during the 4-month evaluation period remained stable during the 8-month follow-up period, with the high-dose regimen continuing to provide greater benefits in most efficacy measures. CsA CE was well tolerated. Treatment-related treatment-emergent adverse events during the 12-month study were reported in 15 (20.8%) and 11 (15.7%) of the CsA CE high-dose and low-dose patients, respectively, most commonly instillation site pain (13.9% and 7.1%, respectively). Laboratory data, vital signs, slit lamp examination, best-corrected distance visual acuity, and intraocular pressure raised no safety concerns.

• CONCLUSIONS: Improvements in keratitis, symptoms, and QoL achieved after CsA CE treatment for 4 months remained stable over the 8-month follow-up period. CsA continued to maintain a favorable safety profile. (Am J Ophthalmol 2020;212:116–126. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

VERNAL KERATOCONJUNCTIVITIS (VKC) IS A RARE but severe form of ocular allergic conjunctivitis, which presents before 10 years of age in 80% of cases, with boys affected 3-4 times more often than girls.[1,2] VKC occurs globally, most commonly in temperate zones in the Mediterranean area, Middle East, Africa, Central America, and Indian subcontinent, and less frequently in Northern Europe, North America, and Australia.[1,3,4] VKC is characterized by allergic inflammation of the ocular surface, with key signs and symptoms including photophobia, conjunctival hyperemia, itching, stringy mucous discharge, giant papillae on the upper tarsal conjunctiva (Figure 1), gelatinous infiltrates on the corneoscleral limbus with white-yellow nodules (Horner-Trantas dots), superficial punctate keratitis, and corneal shield ulcers.[2,5–7] Persistent keratitis and other corneal complications occur in an estimated 25%-50% of cases, potentially leading to vision loss.[1,8] Severe VKC may cause limitations in daily activities, school work, and psychosocial relationships, thereby adversely affecting health-related quality of life (QoL).[2,9]

Symptoms often follow a seasonal course but also may be perennial, chronic, or with acute exacerbations.[5] They are thought to reflect both an IgE- and non-IgE-mediated response, in which Th2 cells and Th2-derived cytokines may induce the IgE switch (about 50% of patients are IgE positive) and activate mast cells, eosinophils, neutrophils, and possibly resident cells, including corneal keratocytes and conjunctival fibroblasts.[2,3,10,11] As a result, numerous

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mediators are released from these cells, causing ocular inflammation and remodeling. A variety of treatments are available for 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.[5,12] Topical corticosteroids are effective in moderate-to-severe disease, but their use is limited to short courses because of their tendency to promote severe adverse effects such as cataracts, glaucoma, and secondary corneal infections.[1,5] Topical cyclosporine A (CsA) is effective in reducing the signs and symptoms of VKC as well as the need for corticosteroids[13–16] and has shown the potential to prevent or limit subsequent seasonal reactivation of the disease.[17] Mechanistically, CsA is thought to control ocular surface inflammation in VKC by inhibiting Th2 proliferation, interleukin-2 production, immune cell number increases, and the effects of mediators on the ocular surface and conjunctiva.[7,12]

CsA is a lipophilic substance that is practically insoluble in water, and therefore must be delivered topically to the eye in a lipid-based system.[18] 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.[19] When instilled in the eye, the positively charged nanodroplets in the cationic emulsion are attracted to the negatively charged cell membranes, which leads to increased residence time at the ocular surface.[20] As a result, CsA CE improves the ocular bioavailability of CsA. CsA CE was shown to be effective in treating severe keratitis in dry eye with a favorable safety and tolerability profile in randomized clinical studies.[21–23] In the phase 3 VErnal KeratoconjunctiviTIs Study (VEKTIS), CsA CE was shown to be significantly more effective than the CE vehicle in improving keratitis, key symptoms, and QoL in children and adolescents with severe VKC during a 4-month evaluation period. The study's primary endpoint of superiority of CsA CE over vehicle for a composite 4-month score reflecting severity of keratitis, need for rescue medication, and occurrence of corneal ulceration was achieved.[24] Herein, we present results from the 8-month double-masked safety follow-up period of the VEKTIS.

METHODS

• **STUDY DESIGN:** The study design of VEKTIS (Figure 2) has been published previously.[24] Briefly, VEKTIS was a prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-arm, phase 3 study conducted from April 2013 to February 2016 at 51 sites in 11 countries

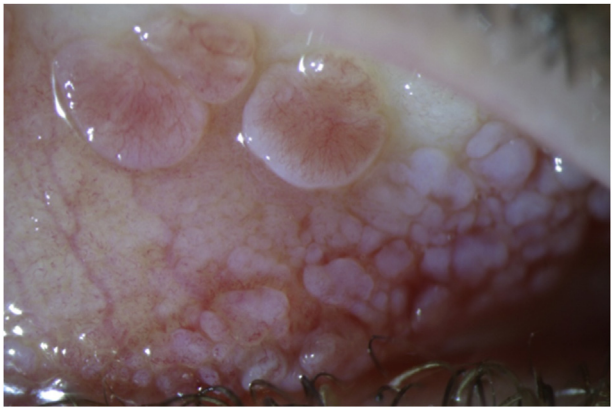

FIGURE 1. Giant papillae on the upper tarsal conjunctiva in a patient with vernal keratoconjunctivitis.

(Spain, France, India, Italy, Israel, United States, Greece, Hungary, Portugal, Croatia, Germany). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees and regulatory agencies (as appropriate) approved the study protocol before the study was initiated. A parent or legal guardian for each patient provided written informed consent, and the patient provided assent when possible. VEKTIS was registered at ClinicalTrials.gov (identifier number NCT01751126).

VEKTIS included a 4-month efficacy/safety evaluation period and an 8-month double-masked safety follow-up period. At each site, patients were enrolled early during the allergy season to allow the 4-month evaluation period to occur during the VKC season. Eligible patients were randomly assigned in a 1:1:1 ratio to receive 1 drop of CsA CE 0.1% (1 mg/mL) 4 times daily (QID; high-dose), 1 drop of CsA CE 2 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.

Following completion of the 4-month evaluation period, CsA CE patients who had enrolled early in the course of the VKC allergy season during which the study was being conducted, and who still presented with signs and symptoms of VKC according to the investigator's judgment, were allowed to continue on their assigned active treatment in a double-masked fashion. Patients initially assigned to the vehicle group who still presented with signs and symptoms of VKC after the 4-month evaluation period were allowed to switch to active treatment (1 drop of CsA CE QID or 1 drop of CsA CE BID plus 1 drop of vehicle BID), which was predetermined during the initial randomization. Patients who experienced a recurrence of active VKC or a worsening of VKC symptoms following discontinuation of study treatment outside of the VKC allergy season were allowed to resume study treatment for the

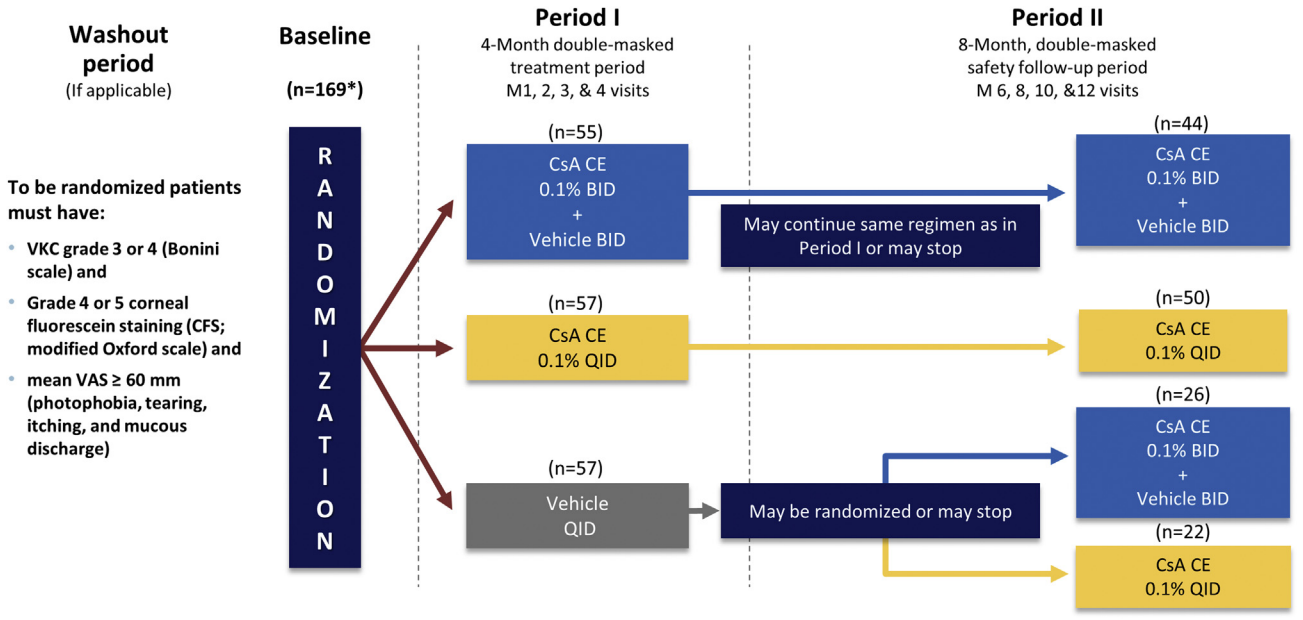

FIGURE 2. VEKTIS design. *n = 101 recruited in Europe. BID = twice per day, CFS = corneal fluorescein staining, CsA CE = cyclosporine A 0.1% (1 mg/mL) cationic emulsion, M = months, QID = 4 times per day, VAS = visual analog score, VEKTIS = VErnal KeratoconjunctiviTIs Study; VKC = vernal keratoconjunctivitis.

remaining months of the follow-up period and were assigned to 1 of the 2 active treatment regimens as described above. Study visits were scheduled every 4 weeks during the evaluation period, and then every 8 weeks during the follow-up period.

Rescue medication (dexamethasone 0.1% QID for up to 5 days) was permitted in the event of keratitis (corneal fluorescein staining [CFS] score) worsening by ≥1 grade or maintenance of the CFS score for 2 months at the entry level, and/or symptom worsening of ≥10 mm (on a 0-100-mm visual analog scale [VAS]) for ≥1 of the 4 main VKC symptoms plus worsening or maintenance at the entry level of the mean 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 during the evaluation period, and a maximum of 4 courses was allowed between visits during the follow-up period. Use of artificial tears (all unpreserved brands permitted) was recorded in a patient diary.

• **PATIENTS:** Eligibility criteria for VEKTIS have been described previously.[24] Briefly, male or female patients aged 4 to <18 years were eligible if they had active severe VKC (grade 3 or 4 on the Bonini scale[25]) with severe keratitis (CFS score of grade 4 or 5 on the modified Oxford scale[26] [7-point scale; range of 0-5: absence of staining to greatest severity; individual grades: 0, 0.5, 1, 2, 3, 4, 5]), had experienced ≥1 recurrence of VKC during the previous year, and had 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). Topical or systemic corticosteroids within 1 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. 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.

• **SAFETY:** Local ocular tolerance during the 8-month follow-up period was evaluated by external examination and biomicroscopy using a slit lamp at each study visit (month 6 [week 24], month 8 [week 32], month 10 [week 40], and month 12 [week 48]). 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. Ocular and systemic adverse events were monitored throughout the study. Best-corrected distance visual acuity (BCDVA) and intraocular pressure (IOP) by tonometry

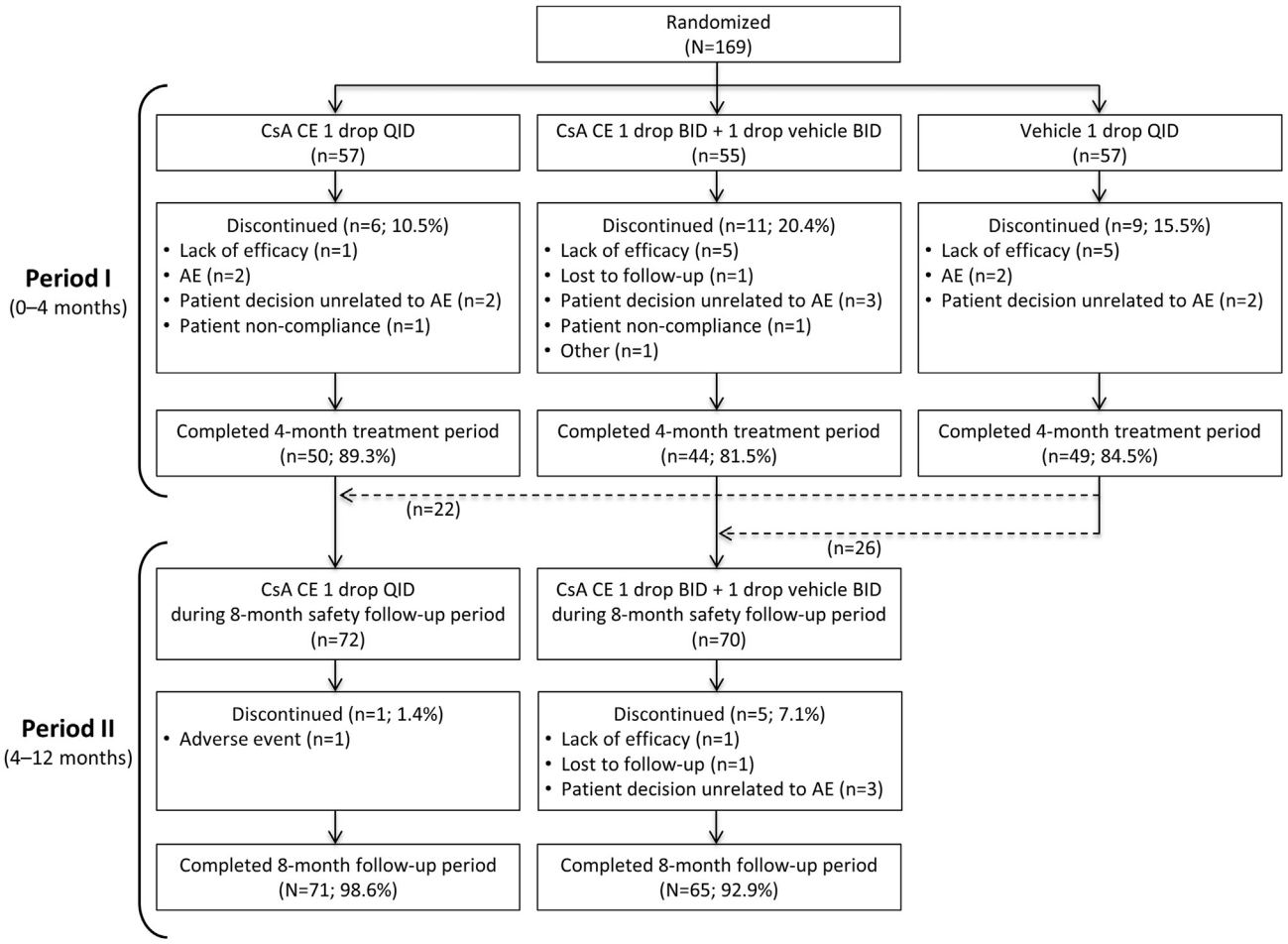

FIGURE 3. VEKTIS patient disposition. *One patient was randomized to CsA CE 1 drop QID but incorrectly received vehicle initially. AE = adverse event; BID = twice per day, CsA CE = cyclosporine A cationic emulsion 0.1% (1 mg/mL), N = number of patients, QID = 4 times per day; VEKTIS = VErnal KeratoconjunctiviTIs Study.

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, 4, and 12.

• **EFFICACY ASSESSMENTS:** Efficacy variables assessed during the 8-month follow-up period included CFS score, use of rescue therapy, occurrence of corneal ulceration, VAS scores for the 4 main VKC symptoms, and QoL over the preceding 2-week period (assessed using the Symptoms and Daily Activities domains of the QUICK questionnaire).[9] Both the VAS and QUICK assessments were performed at the beginning of study visits, before a medical history or any other study-related assessments. All of the preceding were assessed at each of the 4 follow-up period study visits, with the exception of the QUICK questionnaire (month 12 only). In addition, the investigator global evaluation of efficacy (IGEE), in which the investigator rated the overall effect of study medication using a 4-point scale ranging from 0 (unsatisfactory) to 3 (very satisfactory), was performed only at month 12 during the follow-up period.

• **STATISTICAL ANALYSIS:** All safety parameters were evaluated descriptively. Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Because the follow-up period was designed to obtain safety data and was not vehicle controlled, efficacy parameters obtained at months 6, 8, 10, and 12 were also evaluated using descriptive statistics. The descriptions of the 8-month efficacy data are limited to analyses of patients who did not stop their treatment at month 4 and continued it in a continuous way through month 12 (subgroup B) and patients who used the active treatment in an intermittent manner during the 8-month follow-up period (subgroup C). Because of the small number of patients who stopped treatment at month 4 and never used it again until month 12 (subgroup A), these data were not included.

TABLE 1. Demographic and Baseline Characteristics

Characteristic	FAS Cohort[a]			Follow-Up Cohort	
	CsA CE QID (n = 56)	CsA CE BID (n = 54)	Vehicle (n = 58)	CsA CE QID (n = 72)	CsA CE BID (n = 70)
Age, y, mean (SD)	9.1 (3.3)	9.6 (3.4)	8.9 (3.2)	8.9 (3.4)	9.3 (3.2)
Age group					
Age 4-11 y	43 (76.8)	38 (70.4)	46 (79.3)	56 (77.8)	52 (74.3)
Age 12-17	13 (23.2)	16 (29.6)	12 (20.7)	16 (22.2)	18 (25.7)
Sex					
Male	44 (78.6)	42 (77.8)	46 (79.3)	57 (79.2)	53 (75.7)
Female	12 (21.4)	12 (22.2)	12 (20.7)	15 (20.8)	17 (24.3)
Race					
White	40 (71.4)	38 (70.4)	41 (70.7)	51 (70.8)	49 (70.0)
Asian	11 (19.6)	11 (20.4)	13 (22.4)	16 (22.2)	15 (21.4)
Black	3 (5.4)	5 (9.3)	2 (3.4)	4 (5.6)	4 (5.7)
Other	2 (3.6)	0 (0)	2 (3.4)	1 (1.4)	2 (2.9)
Form of VKC					
Limbal	8 (14.3)	2 (3.7)	7 (12.1)	10 (13.9)	7 (10.0)
Tarsal	15 (26.8)	13 (24.1)	13 (22.4)	19 (26.4)	16 (22.9)
Mixed	33 (58.9)	39 (72.2)	38 (65.5)	43 (59.7)	47 (67.1)
Type of VKC					
Seasonal	29 (51.8)	25 (46.3)	21 (36.2)	35 (48.6)	28 (40.0)
Perennial	27 (48.2)	29 (53.7)	37 (63.8)	37 (51.4)	42 (60.0)
Time since diagnosis, y, mean (SD)	3.5 (2.5)	3.6 (2.8)	3.1 (2.6)	3.2 (2.3)	3.5 (2.9)
VKC grade[b]					
Grade 3	32 (57.1)	32 (59.3)	40 (69.0)	45 (62.5)	42 (60.0)
Grade 4	24 (42.9)	22 (40.7)	18 (31.0)	27 (37.5)	28 (40.0)
CFS score[b]					
Grade 4	42 (75.0)	49 (90.7)	54 (93.1)	61 (84.7)	64 (91.4)
Grade 5	14 (25.0)	5 (9.3)	4 (6.9)	11 (15.3)	6 (8.6)
Asthma	12 (21.4)	10 (18.5)	11 (19.0)	14 (19.4)	11 (15.7)

BID = twice per day, CFS = corneal fluorescein staining, CsA CE = cyclosporine A cationic emulsion 0.1% (1 mg/mL), FAS = Full Analysis Set, QID = 4 times per day, SD = standard deviation, VKC = vernal keratoconjunctivitis.

Unless otherwise noted, values are n (%).

[a]Full Analysis Set: 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).

[b]Grade or score of analysis eye; VKC grading by Bonini scale and CFS score by modified Oxford scale.

RESULTS

• **PATIENTS:** A total of 169 patients were initially randomized to study treatment, and subsequently 142 patients entered the safety follow-up period, including 48 patients who were initially allocated to vehicle and then switched to one of the CsA CE regimens (Figure 3). Of the follow-up cohort, 136 patients (95.8%) completed the 12-month study visit. The reasons for discontinuation during the follow-up period were patient decision unrelated to an adverse event (2.1%), lack of efficacy (0.7%), adverse event (0.7%), and patient loss to follow-up (0.7%). Notably, the percentage of patients discontinuing early was lower in the CsA CE high-dose group compared with the CsA CE low-dose group during both the 4-month evaluation and 8-month follow-up periods.

Demographic and baseline clinical characteristics in both CsA CE groups in the follow-up period were generally well balanced and consistent with those in the 4-month efficacy evaluation period (Table 1). For the cohort participating in the safety follow-up period, the mean age was 9.1 years (range, 4-17 years), and the mean time since VKC diagnosis was 3.4 years. Most patients were males (77.5%), white (70.4%), had the mixed form of VKC (ie, both limbal and tarsal signs; 63.4%), and had perennial VKC (88.0%). Asthma was present in 17.6% of the overall follow-up population. In the analysis eye, the majority had VKC grade 3 (61.3%) and a CFS score of 4 (88.0%) at baseline.

During the follow-up period, 84 patients (59.2%), including 42 in the CsA CE high-dose group and 42 in the CsA CE low-dose group, continued to use study

TABLE 2. Summary of Treatment-Emergent Adverse Events (TEAEs) During 8-Month Follow-up Period and Entire 12-Month Study

Parameter	Follow-Up Period (Months 4-12)		Entire Study (Months 0-12)	
	CsA CE QID, n (%) (n = 72)	CsA CE BID, n (%) (n = 70)	CsA CE QID, n (%) (n = 72)	CsA CE BID, n (%) (n = 70)
Patients with ≥1 TEAEs	27 (37.5)	23 (32.9)	42 (58.3)	35 (50.0)
Patients with treatment-related TEAEs	4 (5.6)	6 (8.6)	15 (20.8)	11 (15.7)
Patients with serious TEAEs	1 (1.4)	0 (0)	3 (4.2)	1 (1.4)
Discontinuations due to TEAEs	1 (1.4)	0 (0)	1 (1.4)	0 (0)
Discontinuations due to treatment-related TEAEs	1 (1.4)	0 (0)	1 (1.4)	0 (0)
Most common TEAEs				
Eye disorders[a]				
Ocular hyperemia	4 (5.6)	0 (0)	4 (5.6)	1 (1.4)
Eye pruritus	3 (4.2)	1 (1.4)	3 (4.2)	1 (1.4)
Corneal leukoma	1 (1.4)	0 (0)	2 (2.8)	1 (1.4)
Ulcerative keratitis	0 (0)	1 (1.4)	2 (2.8)	1 (1.4)
Eye irritation	0 (0)	1 (1.4)	0 (0)	2 (2.9)
Ocular discomfort	2 (2.8)	0 (0)	2 (2.8)	0 (0)
Other TEAEs[b]				
Instillation site pain	2 (2.8)	2 (2.9)	10 (13.9)	5 (7.1)
Instillation site pruritus	1 (1.4)	2 (2.9)	5 (6.9)	4 (5.7)
Headache	2 (2.8)	1 (1.4)	5 (6.9)	1 (1.4)
Instillation site erythema	0 (0)	1 (1.4)	3 (4.2)	2 (2.9)
Nasopharyngitis	3 (4.2)	2 (2.9)	3 (4.2)	6 (8.6)
Influenza	4 (5.6)	0 (0)	4 (5.6)	0 (0)
Cough	2 (2.8)	0 (0)	4 (5.6)	0 (0)
Pyrexia	1 (1.4)	1 (1.4)	1 (1.4)	3 (4.3)

BID = twice daily, CsA CE = cyclosporine A cationic emulsion 0.1% (1 mg/mL), QID = 4 times daily, TEAEs = treatment-emergent adverse events.

[a]Eye disorders occurring in 2 or more patients in any group.

[b]Other TEAEs occurring in 3 or more patients in any group.

treatment in a continuous manner (subgroup B); the mean duration of treatment during this period was 231.5 and 215.4 days, respectively. Forty-nine patients (34.5%), including 26 in the CsA CE high-dose group and 23 in the CsA CE low-dose group, used study treatment in an intermittent manner (subgroup C); in these patients, the mean duration of study drug use following reintroduction was 132.3 and 126.4 days, respectively. The remaining 9 patients (6.3%) stopped study treatment at month 4 and did not use it again during the follow-up period (subgroup A).

• **SAFETY:** The safety findings during the 4-month evaluation period were reported previously.[24] Herein, safety results are reported for the 8-month follow-up and entire 12-month study for the 142 patients who entered the follow-up period (Table 2). Over the 12-month study, the CsA CE high-dose group compared with the low-dose group had a slightly higher rate of TEAEs (58.3% and 50.0%, respectively) and treatment-related TEAEs (20.8% and 15.7%, respectively) (Table 2). The most common TEAEs related to study medication in the CsA CE high-dose group were instillation site pain (13.9%) and instillation site pruritus (6.9%); the most common treatment-related TEAE in the low-dose group was instillation site pain (7.1%). Overall, 4 patients experienced a serious TEAE, none of which was assessed as related to the study treatment. During the follow-up period, 1 patient (1.4%) in the CsA CE high-dose group withdrew because of a TEAE (eye pain); no other patients withdrew from either group due to TEAEs.

There were no clinically relevant changes in alanine aminotransferase, aspartate aminotransferase, creatinine, blood pressure, or pulse or respiratory rates over the 4-month evaluation period or 8-month follow-up period. At the month 12/early termination visit, CsA blood levels were measurable in 12 patients (17.6%) in the CsA CE high-dose group and in 5 patients (8.2%) in the CsA low-dose group. The maximum blood CsA concentration during the follow-up period in the high-dose and low-dose groups were 0.291 and 0.180 ng/mL, respectively. These amounts are considered to be negligible.

BCDVA improvements observed during the 4-month evaluation period remained stable during the follow-up

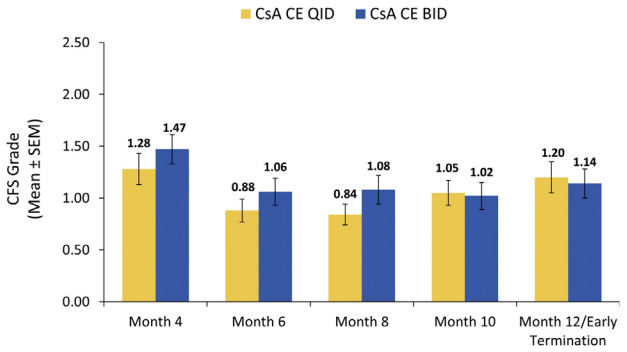

FIGURE 4. Mean CFS scores during the 8-month follow-up period. Patients in the CsA CE QID (high-dose) and CsA CE BID (low-dose) groups included those who received high-dose and low-dose treatment, respectively, during the initial 4-month, vehicle-controlled treatment period and continued on their original treatment, as well as those who received vehicle during the 4-month period and were subsequently rerandomized to either high-dose or low-dose treatment for the 8-month follow-up period. Error bars represent standard error of the mean (SEM). BID = twice per day, CFS = corneal fluorescein staining, CsA CE = cyclosporine A 0.1% (1 mg/mL) cationic emulsion, QID = 4 times per day.

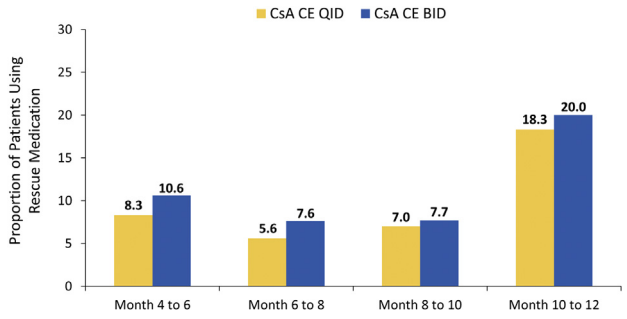

FIGURE 5. Percentage of patients using rescue medication during each 2-month interval of the follow-up period. Patients in the CsA CE QID (high-dose) and CsA CE BID (low-dose) groups included those who received high-dose and low-dose treatment, respectively, during the initial 4-month, vehicle-controlled treatment period and continued on their original treatment, as well as those who received vehicle during the 4-month period and were subsequently rerandomized to either high-dose or low-dose treatment for the 8-month follow-up period. BID = twice per day, CsA CE = cyclosporine A 0.1% (1 mg/mL) cationic emulsion, QID = 4 times per day.

period. The mean change in BCDVA from month 4 to the month 12/early termination visit was –0.020 (95% confidence interval [CI]: –0.058, 0.017) in the CsA CE high-dose group and –0.015 (95% CI: –0.063 to 0.034) in the CsA low-dose group. IOP remained stable over the course of the study. The results of the BCVDA, IOP, and slit lamp examinations did not raise any safety concerns.

• **EFFICACY:** The primary efficacy endpoint for the initial 4-month treatment period of VEKTIS was met as previously reported.[24] The reductions in CFS score achieved with CsA CE during the 4-month evaluation period were maintained during the 8-month follow-up period (Figure 4). Among patients who received active treatment in the follow-up period and used it in a continuous fashion (subgroup B), the high-dose group showed an improvement in CFS score from month 4 to month 6, with a mean change from baseline ± standard deviation (SD) of –0.50 ± 0.91. Subsequently, the CFS score remained stable with changes from baseline of approximately –0.55 until month 12/early termination. The same general trend was seen for the low-dose group, with a mean change from baseline of –0.54 ± 1.23 at month 6. Notably, the CFS score showed further improvement, with changes from baseline of up to –0.96 ± 1.10 at month 10. Among patients who were allocated to the vehicle group during the initial 4-month evaluation period and who were switched to CsA CE during the follow-up period and used the active treatment in a continuous fashion, the switch was associated with an improvement in CFS score during the follow-up period; the mean change from baseline at the month 12/early termination visit was –1.27 ± 1.36 with CsA CE high dose and –0.93 ± 1.71 with CsA CE low dose. Among patients who received active treatment in the follow-up period and used it in an intermittent fashion (subgroup C), further improvement of the CFS score occurred with changes from baseline to month 6 of –0.33 ± 1.02 in the high-dose group and –0.22 ± 0.91 in the low-dose group. However, at month 8, changes from baseline started to become more positive (indicating an increase of the CFS score) until the month 12/early termination visit.

The majority of patients (≥92% in the CsA CE high-dose group and ≥89% in the CsA CE low-dose group) did not use rescue medication during each 2-month interval from month 4 to month 10 (Figure 5). During the last 2-month interval (month 10 to month 12), ≥80% of patients in each group did not use rescue medication. The shift toward increased use of rescue medication during this last interval was driven by patients who used CsA CE intermittently: 30.8% and 36.4% of patients receiving CsA CE high-dose and low-dose intermittently, respectively, required rescue medication. In contrast, among patients receiving CsA CE in a continuous manner, 12.2% in the high-dose and 13.2% in the low-dose group required rescue medication. Improvements in VAS scores for the 4 key VKC symptoms observed during the 4-month evaluation period[24] were maintained and the scores remained stable during the 8-month follow-up period (Figure 6). In patients who did not stop study treatment at month 4 and used it in a continuous fashion, additional symptom improvement was seen during the follow-up period, especially in those switching from vehicle to CsA CE

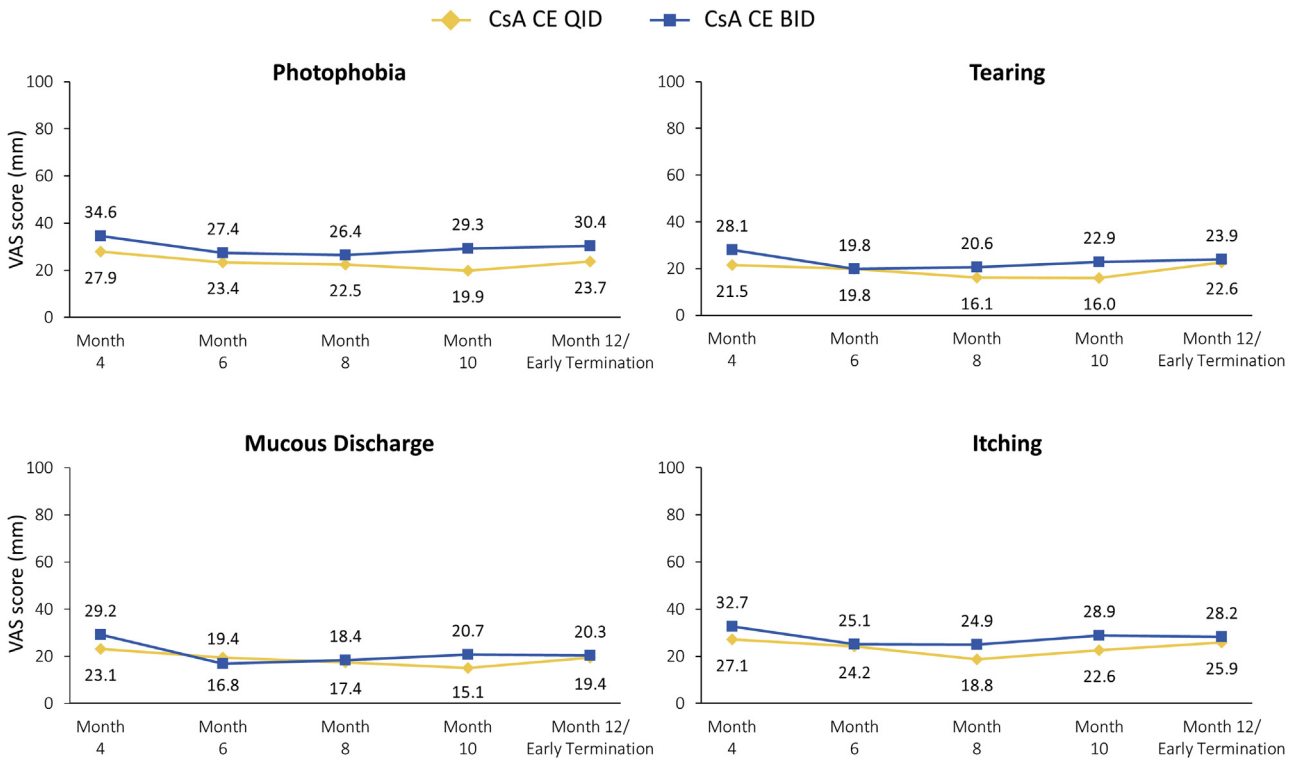

FIGURE 6. Key VKC symptoms measured on a 100-mm visual analog scale (VAS) during the 8-month follow-up period. Higher VAS scores indicate greater severity of symptoms. Patients in the CsA CE QID (high-dose) and CsA CE BID (low-dose) groups included those who received high-dose and low-dose treatment, respectively, during the initial 4-month, vehicle-controlled treatment period and continued on their original treatment, as well as those who received vehicle during the 4-month period and were subsequently rerandomized to either high-dose or low-dose treatment for the 8-month follow-up period. BID = twice per day, CsA CE = cyclosporine A 0.1% (1 mg/mL) cationic emulsion, QID = 4 times per day, VKC = vernal keratoconjunctivitis.

treatment. In patients using CsA CE intermittently during the follow-up, there was no improvement of symptoms for the total groups.

Improvements in QoL reported for the initial 4-month treatment period (assessed by Symptoms and Daily Activities domain scores on the QUICK questionnaire)[24] were maintained, and scores were stable during the follow-up period (Figure 7). In the CsA CE high-dose group, the mean Symptoms domain score was 25.2 (95% CI: 21.2, 29.3) at month 4 and 26.2 (95% CI: 21.4, 31.1) at the month 12/early termination visit, whereas the Daily Activities domain scores at these time points were 3.3 (95% CI: 1.5, 5.1) and 4.7 (95% CI: 2.5, 7.0), respectively.

Investigators provided a positive global assessment of the effect of study treatment in most patients. IGEE ratings of satisfactory or very satisfactory (2 or 3 on a scale from 0 to 3) at month 4 were given for a significantly higher proportion of patients in the CsA CE high-dose group (85.7%) and low-dose group (86.0%) compared with the vehicle group (68.8%) ($P = .080$ for both CsA CE groups vs vehicle). These positive assessments were maintained during the follow-up period. At the month 12/early termination visit, IGEE ratings of satisfactory or very satisfactory were given for 91.7% of patients in the CsA CE high-dose group and 84.4% of patients in the CsA CE low-dose group.

DISCUSSION

THE DOUBLE-MASKED, PHASE 3 VEKTIS TRIAL DEMONstrated that CsA CE was effective in the treatment of children and adolescents with severe VKC, with a favorable safety profile. As previously reported, both CsA CE high dose and CsA CE low dose were superior to vehicle in improving the primary efficacy endpoint for the initial 4-month treatment period, a composite measure based on CFS score with penalties for rescue dexamethasone use and corneal ulceration, during the initial 4-month evaluation period.[24] The efficacy of CsA CE was mainly driven by a reduction in CFS score, reflecting less corneal involvement and damage (and consequentially less symptoms), and to a lesser extent, by a reduction in rescue dexamethasone usage. In addition, the high-dose regimen was shown to more consistently yield statistically significant improvements in VKC symptoms and patient QoL

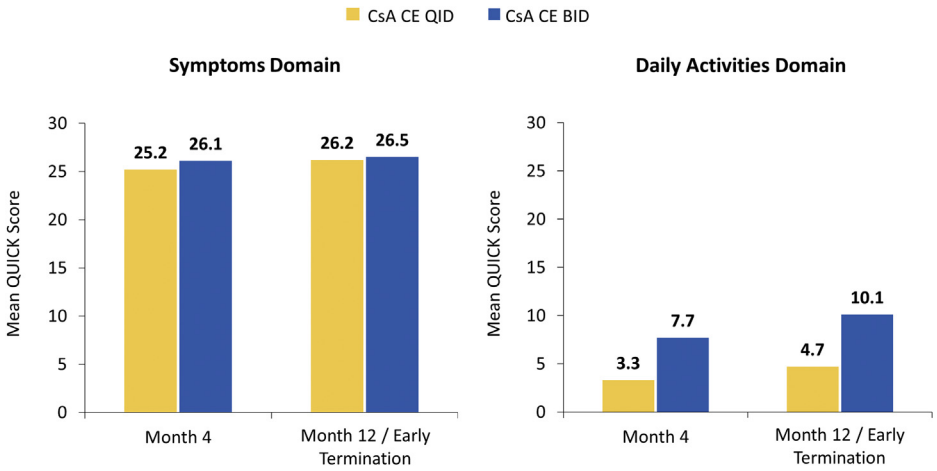

FIGURE 7. QUICK questionnaire scores at month 4 and month 8. Higher scores indicate poorer quality of life. Patients in the CsA CE QID (high-dose) and CsA CE BID (low-dose) groups included those who received high-dose and low-dose treatment, respectively, during the initial 4-month, vehicle-controlled treatment period and continued on their original treatment, as well as those who received vehicle during the 4-month period and were subsequently rerandomized to either high-dose or low-dose treatment for the 8-month follow-up period. BID = twice per day, CsA CE = cyclosporine A 0.1% (1 mg/mL) cationic emulsion, LS = least-squares, QID = 4 times per day, VKC = vernal keratoconjunctivitis.

(assessed by VAS and the QUICK questionnaire, respectively) vs vehicle as compared with low-dose CsA CE. The present results from the 8-month, non-vehicle-controlled, follow-up period, in which patients received either high-dose or low-dose CsA CE in a double-masked fashion, extend these findings. The benefits of CsA CE on CFS and rescue medication use remained stable during the follow-up period. The increased use of rescue medication in the month 10-12 period may reflect the initiation of a new VKC season. Of note, use of rescue medication was notably lower among patients who used CsA CE continuously vs intermittently, suggesting that continuous use may have limited the need for rescue medication during this time. Similarly, the benefits of CsA CE on key VKC symptoms, QoL, and the IGEE reported during the 4-month evaluation period remained stable during the follow-up period. Thus, the efficacy of CsA CE over a 12-month period was supported by both investigator-reported measures (CFS score and IGEE) and patient-reported measures (symptoms and QoL). These findings are consistent with previous VKC studies with other CsA formulations, in which clinical benefits were maintained with continued treatment.[15,27]

During the follow-up period, patients were allowed to use CsA CE in a continuous or intermittent manner, or to discontinue study treatment. The proportion of patients who used CsA CE in a continuous manner (n=84; 59.2%) was generally comparable to the proportion with perennial VKC (n=79; 55.6%). Likewise, the proportion either using CsA CE intermittently (n=49; 34.5%) or discontinuing treatment (n=9; 6.3%) was comparable to the proportion with seasonal VKC (n=63; 44.4%). Interestingly, symptom VAS scores worsened during the follow-up period in those who used CsA CE intermittently, whereas continued symptom improvement was reported in those using CsA CE in a continuous manner, particularly in the subset switched from vehicle to CsA CE. Similar trends were observed for the CFS data: after initial improvement at the month 6 visit, the intermittent use population experienced increasing (ie, worsening) CFS scores over time during the follow-up period, whereas scores tended to remain stable or improve after month 6 for the continuous use population. In general, trends with respect to continuous vs intermittent use were not consistently apparent across all efficacy parameters, and the findings cited above may simply reflect the underlying VKC type (ie, perennial vs seasonal). Nevertheless, it should be noted that even seasonal VKC symptoms may persist for longer than 4 months, and that many of the seasonal VKC patients completing month 12 of the follow-up were likely entering the start of a second VKC season. CsA CE treatment in this population of patients with severe VKC was able to sustain improvements in VKC signs or symptoms and QoL with minimal use of corticosteroid rescue medication. This is clinically significant, given the severe adverse events associated with chronic, long-term use of corticosteroid treatment and the fact that even the seasonal form of VKC can persist for 6-8 months, and the disease (seasonal or perennial) can last for 5-10 consecutive years. In addition, our findings suggest the potential for prolonged use of CsA CE to prevent or limit further seasonal reactivation of VKC, as was suggested in a previous study of topical CsA.[17] Taken as a whole, the results from the follow-up period support continued use of CsA CE when necessary

to maintain symptom control and minimize corneal damage.

The follow-up period was primarily designed to collect safety data on longer-term use of CsA CE. The safety data for the 8-month follow-up period, as well as for the entire 12-month study period, were consistent with the safety profile of topically applied CsA. No unexpected safety findings were observed. The rates of TEAEs for the entire 12-month study period were, in general, proportionately higher than those during the 8-month follow-up period, particularly for instillation site pain, pruritus, and erythema, suggesting that these local events predominantly occur early during CsA CE treatment, and that event rates then decline during continued use. In contrast, ocular hyperemia was detected in 4 patients in the CsA CE high-dose group during the follow-up period (as compared with no cases reported during the initial 4-month period) and may reflect a more delayed TEAE. Overall, TEAEs rarely led to discontinuation of CsA CE, with only 1 patient stopping treatment because of a TEAE during the follow-up period. Importantly, long-term use of CsA CE was not associated with clinically meaningful changes in visual acuity, slit lamp examination findings, or IOP. The latter is notable given that patients had access to the use of topical dexamethasone as rescue therapy. Additionally, topical CsA CE instillation in the eye was associated with negligible systemic exposure to CsA, with no clinically relevant changes in markers of kidney function.

Limitations of the initial randomized, vehicle-controlled 4-month treatment period for VEKTIS have been previously discussed.[24] Some additional limitations should be considered for the present analysis. First, the follow-up period did not include a control group. It should be noted, however, that the primary objective of the 8-month follow-up period was to evaluate the long-term safety and tolerability of CsA CE, and that the efficacy data generated during this period were only descriptive, as all patients who required treatment received CsA CE. Consequently, these results must be confirmed in subsequent studies. Second, the pattern of study treatment use during the follow-up period was not consistent for all patients as some used it continuously, others used it intermittently, and a small number discontinued it altogether. However, this pattern of use is reflective of how CsA CE would be used in a real-world clinical practice setting after the VKC season is over (ie, not all patients with perennial disease may receive year-long therapy).

In conclusion, the improvements in keratitis, symptoms, and QoL achieved with CsA CE during the initial 4-month evaluation period were maintained during the subsequent 8-month follow-up period, with both dosing regimens exhibiting favorable safety profiles throughout the year-long exposure. Taken together, these results provide further evidence that topical CsA CE is a viable therapeutic option for children and adolescents with severe VKC.

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