Improvements in Signs and Symptoms of Severe Vernal Keratoconjunctivitis in Patients Treated With 0.1% Ciclosporin A Cationic Emulsion: Results From the VEKTIS Study

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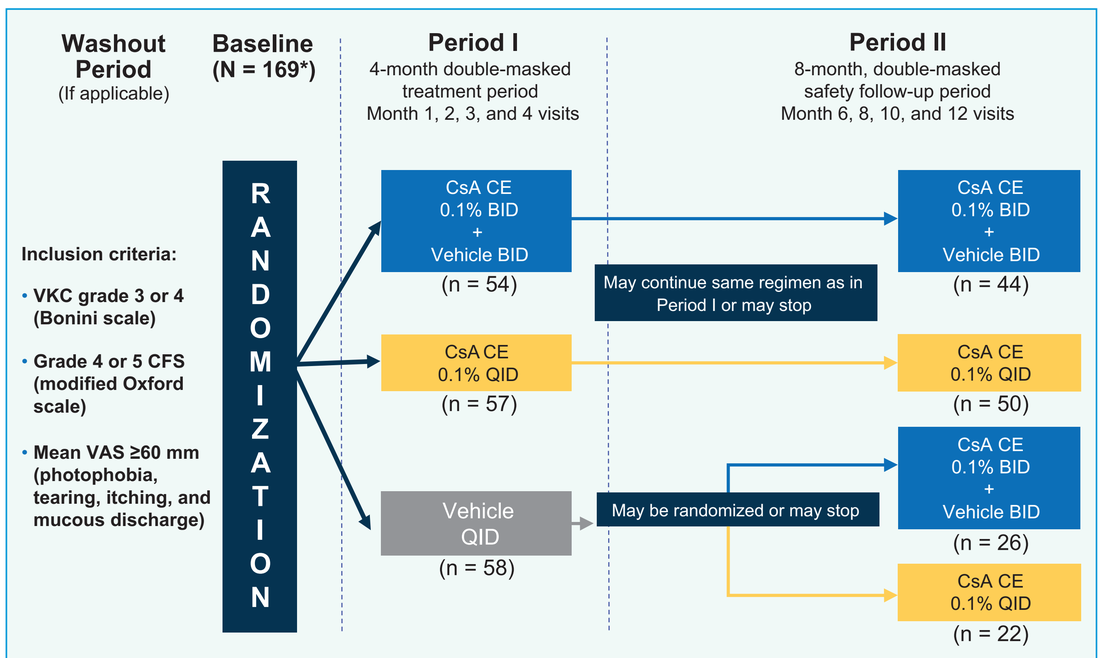
Background

- Vernal keratoconjunctivitis (VKC) is a rare, but severe form of ocular allergic conjunctivitis, occurring mainly in children. Symptoms include itching, grittiness, photophobia, and tearing, which are particularly disabling. Keratitis (which occurs in up to 50% of cases) and shield ulcers are sight-threatening complications.[1]
- 0.1% (1 mg/mL) ciclosporin A cationic emulsion (CsA CE) for topical ocular use is a cationic oil-in-water emulsion that remains longer on the ocular surface than a conventional CsA formulation, thereby optimizing its bioavailability and therapeutic effects.[2-4]
- The VEKTIS study, a phase 3, multicenter, double-masked, vehicle-controlled trial, evaluated the efficacy and tolerability of CsA CE 1-mg/mL eye drops for treating severe VKC in pediatric patients.

Methods

- 169 patients aged 4–8 years who had VKC with severe keratitis were randomized to 4-month treatment with CsA CE 1 mg/mL high-dose (4 times daily), low-dose (twice daily) or to the CE vehicle. This was followed by an 8-month follow-up period during which patients were rerandomized to 1 of the 2 active treatment arms (**Figure 1**).

Figure 1. VEKTIS Study Design



*n=101 recruited in Europe. BID, twice per day; CFS, corneal fluorescein staining; QID, 4 times per day; VAS, visual analogue scale; VKC, vernal keratoconjunctivitis.

- The primary endpoint was a mean composite score that reflected CFS as assessed by the modified Oxford scale, need for rescue medication, and occurrence of corneal ulceration during 4 months. The composite score at 4 months was defined as the mean of the 4 efficacy scores taken at each monthly visit, calculated using the following formula:
  - Patient's score at Month X = CFS (Baseline) – CFS (Month X) + penalty(ies)
  - Penalty for use of rescue medication: –1 (per course, with a maximum of 2 courses between 2 scheduled visits)
  - Penalty for corneal ulceration: –1 (per occurrence)
- Photophobia, tearing, itching and mucous discharge were assessed by patients using a self-administered visual analog scale (VAS; range 0-100).

Results

- Baseline characteristics were comparable among treatment groups (**Table 1**).

Table 1. VEKTIS Patient Baseline Characteristics

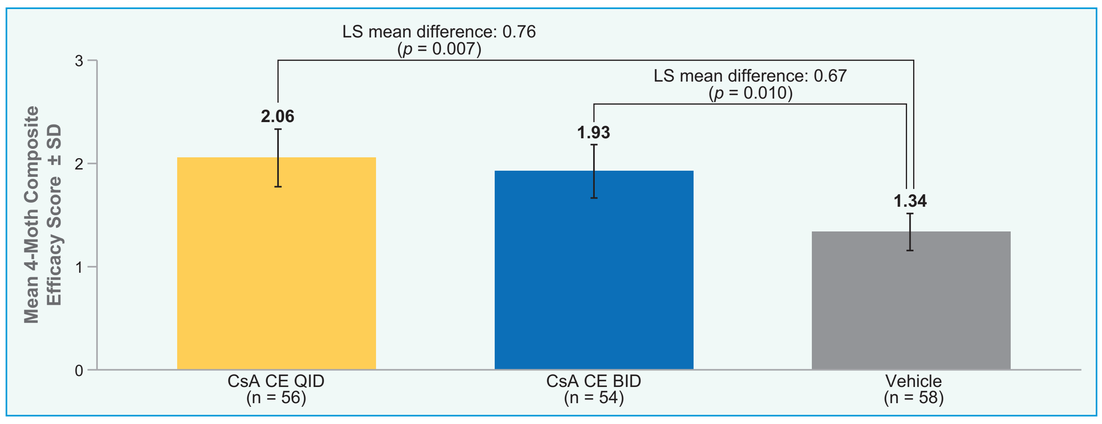
	CsA CE QID (n = 56)	CsA CE BID (n = 54)	Vehicle (n = 58)
Mean age, year (SD)	9.1 (3.3)	9.6 (3.4)	8.9 (3.2)
Male, n (%)	44 (78.6)	42 (77.8)	46 (79.3)
CFS score, n (%)			
Grade 4	42 (75.0)	49 (90.7)	54 (93.1)
Grade 5	14 (25.0)	5 (9.3)	4 (6.9)
Mean symptoms, mm (SD)	75.7 (11.2)	72.6 (9.3)	72.7 (9.5)
Mixed form of VKC (limbal and tarsal), n (%)	33 (58.9)	39 (72.2)	38 (65.5)
Perennial VKC, n (%)	27 (48.2)	29 (53.7)	37 (63.8)
Asthma, n (%)	12 (21.4)	10 (18.5)	11 (19.0)

SD, standard deviation.

Results (continued)

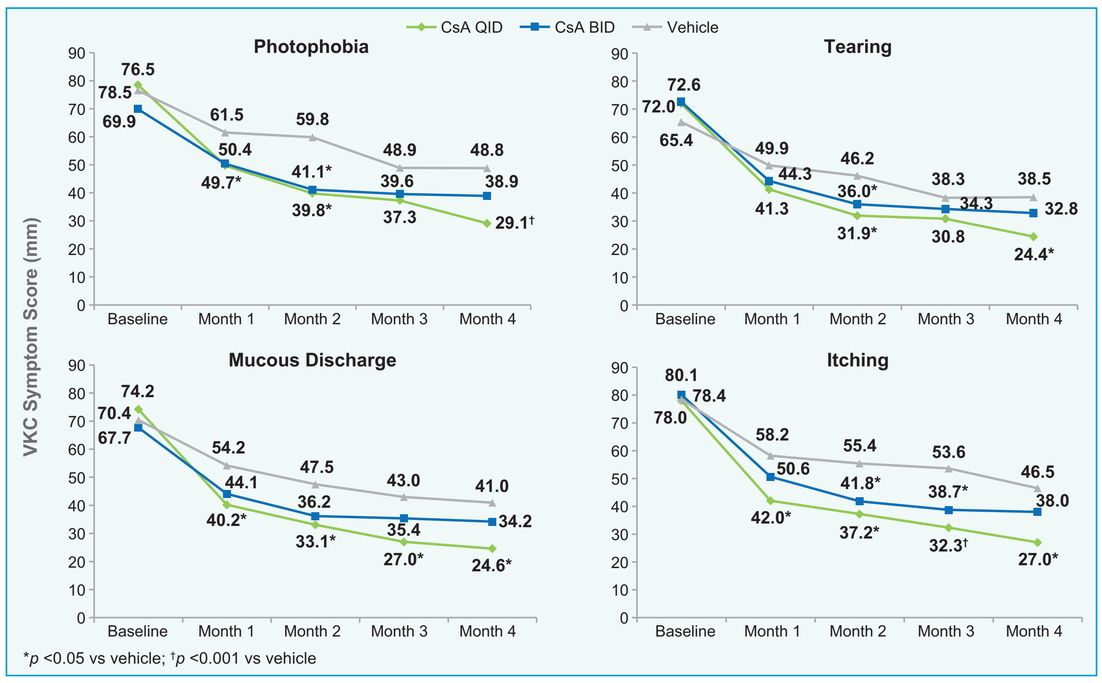
- The primary efficacy endpoint of superiority of active treatment over vehicle over 4 months was met: the difference in the least-squares (LS) mean vs vehicle was statistically significant for both the high-dose group (0.76 [95% confidence interval 0.26–1.27]; $p = 0.007$) and the low-dose group (0.67 [0.16–1.18]; $p = 0.010$) (**Figure 2**).

Figure 2. VEKTIS Primary Endpoint: Average Penalty-Adjusted Composite Score Over 4 Months



- VKC symptoms improved in each group from Months 1-4, with the largest decreases at Month 1 (**Figure 3**).

Figure 3. VKC Symptom Scores Over 4 Months



*p <0.05 vs vehicle; †p <0.001 vs vehicle

- 8-month follow-up demonstrated stability of improvements, especially among patients treated beyond Month 4.

Safety Analysis

- Over the 12-month study period, treatment-emergent adverse events (TEAEs) that were deemed to be related to study medication were reported for 15 patients (21%) in the high-dose total group and 11 (16%) in the low-dose total group.
- The most common TEAEs related to study medication in the high-dose total group were instillation site pain (n = 10 [14%]) and instillation site pruritus (n = 4 [6%]). For the low-dose total group, the most common ocular treatment-related TEAE was instillation site pain (n = 5 [7%]).
- During the 8-month follow-up period, 1 patient (1%) in the high-dose total group withdrew due to a TEAE (eye pain); no other patients withdrew from either the low- or high-dose total group.

Conclusions

- During the initial, 4-month randomized treatment portion of the study, VKC patients who received active high or low doses of CsA CE 0.1% (1 mg/mL) showed significant improvement in CFS scores vs patients receiving vehicle alone. VKC symptoms were also significantly improved with high dose CsA CE vs vehicle over 4 months.
- Improvements in CFS and symptoms scores were maintained over the 12-month course of the study.
- Safety analyses at 12 months after initiation of treatment suggested a favorable tolerability profile for CsA CE.

References: **1.** Bremond-Gignac D, et al. *Br J Ophthalmol.* 2008;92:1097-102; **2.** Daull P et al. *Cornea.* 2013;32:345-54; **3.** Lallemand F, et al. *J Drug Deliv.* 2012;2012:604204; **4.** Vandamme TF.et al. *Prog Retin Eye Res.* 2002;21:15-34.

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Author Disclosures: **A. Leonardi** is a consultant for Santen and Sifi, reports lecture fees for Allergan, Alcon, and Théa, and was an investigator in the SICCANOVE, SANSIKA, and VEKTIS studies. **S. Doan** is a consultant for Alcon, Allergan, Bausch & Lomb, Horus, Santen, and Théa, and was an investigator in the SICCANOVE, SANSIKA, and VEKTIS studies. **M. Amrane** and **D. Ismail** are employees of Santen SAS. **J. Montero** was an investigator in the SICCANOVE, SANSIKA, and VEKTIS studies. **P. Aragona** is a consultant for and has received research grants from Alcon Italia, Allergan, Dompè, Laboratoires Théa, Medivis, Santen, Sifi, Sooft, and TRB Chemedica, and was an investigator in the SICCANOVE and VEKTIS studies. **D. Bremond-Gignac** is a consultant for Alcon, Allergan, Horus, Santen, and Théa, and was an investigator in the SANSIKA and VEKTIS studies.

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