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

3
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38 **VEKTIS study.**

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48

49 **RUNNING HEAD**

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

51

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

54

55 **ABSTRACT**

56 **Background:** Vernal keratoconjunctivitis (VKC) is a chronic, allergic, and
57 potentially severe ocular disease affecting children and adolescents that can lead to
58 impaired quality of life (QoL) and loss of vision.

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

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

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

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

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

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

78 questionnaire) improved in all 3 groups, with significant improvements for high-
79 dose CsA CE versus vehicle.

80 **Conclusions:** The efficacy of high-dose CsA CE in improving keratitis, symptoms,
81 and QoL for those with severe VKC was demonstrated in these study patients. In
82 addition, in this study cohort, CsA CE was well-tolerated.

83

84 **KEY WORDS**

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

88	ABBREVIATIONS AND ACRONYMS
89	AE , adverse event
90	ANCOVA , analysis of covariance
91	ALT , alanine aminotransferase
92	AST , aspartate aminotransferase
93	BCDVA , best corrected distance visual acuity
94	BID , twice daily
95	CE , cationic emulsion
96	CFS , corneal fluorescein staining
97	CI , confidence interval
98	CsA , cyclosporine A
99	CsA CE , cyclosporine A cationic emulsion
100	FAS , full analysis set
101	IGEE , investigator global evaluation of efficacy
102	IOP , intraocular pressure
103	LMMRM , linear mixed model for repeated measures
104	LS , least-squares
105	QID , four times daily
106	QoL , quality of life
107	QUICK , Quality of Life in Children with Vernal Keratoconjunctivitis
108	SEM , standard error of the mean
109	TEAE , treatment-emergent adverse event
110	VAS , visual analogue scale

111 **VKC**, vernal keratoconjunctivitis

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

118

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

129

130 VKC typically occurs in school-age children, with an age of onset prior to 10 years in
131 80% of cases (typical range, 4–7 years), and is reported in males 3 to 4 times more
132 often than in females.^{1,6} VKC often resolves after puberty, although it may persist in
133 adulthood, where the male:female ratio is closer to 1:1.^{4,6} Children with severe VKC

134 may have a poor quality of life (QoL) due to limitations in daily activities/
135 schooling/vacationing, as well as potential psychological/relationship issues.^{1,6,8}

136

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

143

144 Several classes of pharmacological agents are available for the treatment of VKC,
145 including topical mast-cell stabilizers, antihistamines, dual-acting agents with both
146 mast-cell stabilizing and antihistaminic activity, and non-steroidal anti-
147 inflammatory agents. These agents offer short-term relief but do not effectively
148 address the complex immune response that initiates and perpetuates the allergic
149 ocular inflammation, especially in moderate-to-severe VKC.^{4,11} Topical
150 corticosteroids are often necessary in moderate-to-severe disease; though effective,
151 they must be used for short courses due to their tendency to promote severe
152 adverse effects such as cataracts, glaucoma, and secondary corneal infections.^{1,4}

153 Topical cyclosporine A (CsA) is effective in controlling ocular surface inflammation
154 in VKC, and is thought to work by inhibiting Th2 proliferation and interleukin-2
155 production and reducing levels of immune cells and mediators acting on the ocular

156 surface and conjunctiva.¹¹ In clinical studies, CsA has been shown to reduce signs
157 and symptoms of VKC, while providing a steroid-sparing effect.¹²⁻¹⁶
158
159 As a lipophilic substance, CsA is practically insoluble in water and must be delivered
160 topically to the eye in a lipid-based system.¹⁷ Cyclosporine A cationic emulsion 0.1%
161 (1 mg/mL) (CsA CE) is a CsA formulation developed for topical treatment of severe
162 forms of immune-mediated ocular diseases.¹⁸ When a cationic emulsion is instilled
163 in the eye, the positively-charged nanodroplets are attracted to the negatively-
164 charged cell membranes, resulting in increased residence time at the ocular surface;
165 thus CsA CE provides a vehicle for improved ocular bioavailability of CsA.¹⁹ Previous
166 studies have demonstrated the safety and efficacy of CsA CE in treating severe
167 keratitis in dry eye.²⁰⁻²² CsA CE was also shown to provide a significant reduction of
168 VKC signs during a 4-week treatment period, particularly in patients with severe
169 keratitis (Data on File, Santen). The phase 3 VEKTIS study was designed to compare
170 the efficacy and safety of 2 different dosing regimens of CsA CE versus the CE vehicle
171 in children and adolescents with severe VKC.

172

173

METHODS

STUDY DESIGN

174 VEKTIS was a multicenter, randomized, double-masked, vehicle-controlled, parallel-
175 arm, phase 3 study conducted from April 29, 2013, to February 1, 2016, at 51 sites
176 in 11 countries (Spain, France, India, Italy, Israel, United States, Greece, Hungary,
177 Portugal, Croatia, Germany).

179

180 The study was conducted in accordance with ethical principles originating in the
181 Declaration of Helsinki, and in compliance with International Conference on
182 Harmonisation guidelines of Good Clinical Practice and applicable local ethical and
183 legal requirements. Independent ethics committees and regulatory agencies (as
184 appropriate) approved the study protocol prior to study initiation. The parents or
185 legal guardian of each patient provided written informed consent, and the patient
186 provided assent when possible. The study was prospectively registered with
187 ClinicalTrials.gov (NCT01751126).

188

189 The study included a 4-month efficacy/safety evaluation period and an 8-month
190 safety follow-up period (**Fig 1**). Only data from the 4-month treatment period
191 comparing the study drug versus vehicle are reported herein. On Day 0, eligible
192 patients with severe VKC were randomly assigned in a 1:1:1 ratio to receive 1 drop
193 of CsA CE 0.1% (1 mg/mL) four times daily (QID; high-dose), 1 drop of CsA CE two
194 times daily (BID; low-dose) plus 1 drop of vehicle BID, or 1 drop of vehicle QID.
195 Treatment assignments were generated using a computerized randomization
196 schema, stratified by country, and centralized using an interactive web-response
197 system.

198

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

206

207 During the study, rescue medication (dexamethasone 0.1% QID for up to 5 days)
208 was permitted in the event of keratitis (corneal fluorescein staining [CFS] score
209 based on modified Oxford scale²³ (7-point scale; range, 0-5 [absence of staining to
210 greatest severity]; individual grades: 0, 0.5, 1, 2, 3, 4, 5) worsening by ≥ 1 grade or
211 maintenance of the CFS score for 2 months at the entry level, and/or symptom
212 worsening of ≥ 10 mm for ≥ 1 of the 4 VKC symptoms plus worsening or maintenance
213 at the entry level of the mean visual analogue scale (VAS) score for the 4 symptoms.
214 Dexamethasone had to be given at least 30 minutes before or after study
215 medication. A maximum of 2 courses was allowed between study visits.

216

217 **PATIENTS**

218 Eligible patients included males or females aged 4 to <18 years with active severe
219 VKC (grade 3 or 4 on the Bonini scale²⁴) and severe keratitis with a CFS score of
220 grade 4 or 5 on the modified Oxford scale. Patients were required to have
221 experienced ≥ 1 recurrence of VKC during the previous year, and to have a mean

222 score for the 4 main VKC symptoms (photophobia, tearing, itching, and mucous
223 discharge) of ≥ 60 mm on a 0–100 mm VAS (0, no symptoms; 100, comparable to the
224 worst discomfort ever experienced). Enrollment had to occur early during the
225 allergy season for that site in order to allow the 4-month treatment period to occur
226 during the VKC season.

227

228 Subjects were excluded if they had ocular anomalies other than VKC affecting the
229 ocular surface; abnormalities of lid anatomy, nasolacrimal drainage, or blinking
230 function; active ocular infection or history of ocular herpes, varicella-zoster, or
231 vaccinia virus infection; or any ocular disease that would require topical ocular
232 treatment during the study. Presence or history of severe systemic allergy at study
233 entry was also an exclusion criterion. Subjects were not tested with a skin prick test
234 or required to have a specific IgE blood level as part of the inclusion criteria. Topical
235 or systemic corticosteroids within 1 week, topical CsA, tacrolimus, or sirolimus or
236 any systemic immunosuppressive drug within 90 days prior to enrollment, or
237 scraping of the vernal plaque within 1 month or any other ocular surgery within 6
238 months before Baseline were not allowed.

239

240 **EFFICACY ASSESSMENTS**

241 Efficacy was assessed monthly during the 4-month treatment period using a
242 composite score designed to reflect changes in 3 important aspects of the VKC
243 disease process that are known to have a major impact on symptoms and disease
244 progression: (1) keratitis assessed by CFS and scored using the modified Oxford

245 scale (a sign of allergic inflammatory damage to the ocular surface, which impacts
246 on the main symptoms of photophobia, burning, and pain)⁶⁻¹⁰; (2) need for rescue
247 medication (a sign of poor response to study treatment); and (3) occurrence of
248 corneal ulceration (a sign of disease worsening and poor response to treatment;
249 defined for the study as an extensive superficial punctate keratitis with exposure of
250 Bowman's membrane). The composite score at each monthly visit was calculated as
251 the difference in CFS score from Baseline, with penalties of -1 for each course of
252 rescue medication or occurrence of corneal ulceration, as shown below:

- 253 • Patient's score at month X= CFS score (Baseline) – CFS score (Month X) +
254 penalty(ies)
- 255 • Penalty for rescue medication: -1 (per course, with a maximum of 2 courses
256 between 2 scheduled visits)
- 257 • Penalty for corneal ulceration: -1 (per occurrence)

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

260

261 Secondary efficacy endpoints assessed at each monthly visit included the CFS score,
262 use of rescue therapy, occurrence of corneal ulceration, VAS scores for the 4 main
263 VKC symptoms, QoL over the preceding 2-week period (assessed using the
264 Symptoms and Daily Activities domains of the Quality of Life in Children with Vernal
265 Keratoconjunctivitis [QUICK] questionnaire),⁸ and use of artificial tears (all
266 unpreserved brands permitted) as recorded in the patient diary. In addition,
267 responder rate and the investigator global evaluation of efficacy (IGEE) were

268 assessed at Month 4. For the IGEE, the investigator rated the overall effect of study
269 medication using a 4-point scale ranging from 0 (unsatisfactory) to 3 (very
270 satisfactory). Both the VAS and QUICK assessments were performed at the
271 beginning of study visits before a medical history or any other study-related
272 assessments. A patient was considered a responder if their mean CFS score during
273 the last 3 months of treatment was $\leq 50\%$ of the Baseline value, and he/she did not
274 withdraw for a reason possibly due to treatment, did not experience ulceration, and
275 did not use rescue medication during the last 3 months of treatment.

276

277 Other parameters assessed were conjunctival erythema/hyperemia, conjunctival
278 discharge, conjunctival chemosis, papillae, and limbal infiltrates, each evaluated by
279 external examination and biomicroscopy using a slit lamp and graded on a
280 numerical scale. Numerical scales for conjunctival erythema/hyperemia,
281 conjunctival discharge, conjunctival chemosis, papillae, and limbal infiltrates were
282 constructed as follows: For conjunctival erythema/hyperemia, conjunctival
283 discharge, and conjunctival chemosis, 0=Absent; 1=Mild; 2=Moderate; 3=Severe; for
284 papillae, 0=Absent; 1=Mild hyperemic scattered papillae; 2=Moderate diffuse
285 hyperemic swollen papillae; 3=As before but more severe; 4=Hyperemic swollen
286 giant papillae covering the superior tarsal plate; for limbal infiltrates, 0=Absent;
287 1=Mild limbus hyperemia and swelling; 2=Moderate limbus hyperemia and
288 swelling; 3=As before but more severe; 4=360° limbus hyperemia and swelling.

289

290 **SAFETY**

291 Local ocular effects were evaluated by external examination and biomicroscopy
292 using a slit lamp. Anterior chamber inflammation and lens opacification were
293 assessed, each graded on a numerical scale (0-3), as described in the Appendix
294 (available at www.aaojournal.org).

295

296 Ocular and systemic adverse events (AEs) were monitored throughout the study.
297 Best-corrected distance visual acuity (BCDVA) and intraocular pressure (IOP) by
298 tonometry were assessed at each visit. Blood samples for measurement of CsA
299 levels, serum creatinine, alanine aminotransferase (ALT), and aspartate
300 aminotransferase (AST) were collected at Baseline and Months 2 and 4.

301

302 **STATISTICAL ANALYSIS**

303 Efficacy parameters were evaluated in the full analysis set (FAS), which consisted of
304 all randomized patients who received ≥ 1 dose of study medication, and who did not
305 have early withdrawal during the first week for reasons definitely unrelated to
306 study medication (thus resulting in a lack of post-randomization data). For the
307 primary endpoint, the superiority of CsA CE over vehicle was evaluated using an
308 analysis of covariance (ANCOVA) model with treatment, Baseline CFS, and exposure
309 to VKC season as covariates. A Hochberg procedure was used to address multiplicity
310 issues with the 2 active treatment regimens. Additional information regarding
311 statistical procedures is provided in the Appendix (available at
312 www.aaojournal.org).

313

314 **RESULTS**

315 **PATIENTS**

316 A total of 169 patients were randomized to study treatment (**Fig 1**). Of these, 143
317 patients (84.6%) completed the 4-month treatment period. Overall, the most
318 frequent reasons for discontinuation were lack of efficacy (6.5%) and patient
319 decision unrelated to an AE (4.1%). Notably, more patients in the CsA CE low-dose
320 and vehicle groups versus the CsA CE high-dose group withdrew early due to lack of
321 efficacy (9.3%, 8.6%, versus 1.8%, respectively). One randomized patient did not
322 have severe active VKC at Baseline and was therefore excluded from the FAS.

323
324 The demographic and Baseline clinical characteristics of the 3 treatment groups
325 were generally well balanced (**Table 1**). Overall, the mean age was 9.2 years; 78.6%
326 of patients were male; and 70.8% were Caucasian. The mean time since VKC
327 diagnosis was 3.4 years. Most patients (65.5%) had the mixed form of VKC (both
328 limbal and tarsal signs), with perennial VKC diagnosed in 55.4%. The majority had
329 VKC grade 3 (61.9%) and a CFS score of 4 (86.3%) at Baseline (13.7% had a CFS
330 score of 5). Notably, more patients in the CsA CE high-dose group had a CFS score of
331 5 at Baseline versus the other 2 groups. Asthma was present in 19.6% of the overall
332 study population.

333
334 **COMPOSITE EFFICACY SCORE (PRIMARY ENDPOINT)**

335 The composite efficacy score increased (i.e. improved) over the 4-month treatment
336 period in each treatment group (**Fig 2A**). The mean composite score over the entire

337 period (primary endpoint) was 2.06 (95% CI: 1.67–2.45) in the CsA CE high-dose
338 group, 1.93 (95% CI: 1.56–2.30) in the CsA CE low-dose group, and 1.34 (95% CI:
339 1.02–1.67) in the vehicle group (**Fig 2B**). Between-group comparisons favored both
340 active treatments over vehicle; the difference in the least-squares mean for CsA CE
341 high-dose versus vehicle was 0.76 (95% CI: 0.26–1.27; P=0.007), and the difference
342 for CsA CE low-dose versus vehicle was 0.67 (95% CI: 0.16–1.18; P=0.010) (**Table**
343 **2**).

344

345 The CFS score was the main driver of the improvement in the composite primary
346 endpoint, accounting for 70% and 78% of the treatment effect in the CsA CE high-
347 dose and low-dose groups, respectively (**Table 2**). Decreases in rescue medication
348 use accounted for most of the remaining treatment effect (30% in the CsA CE high-
349 dose group; 22% in the CsA CE low-dose group). The proportion of patients with ≥ 1
350 course of rescue medication over the 4 months was 32.1%, 31.5%, and 53.4% in the
351 QID, BID, and vehicle groups, and the mean number of rescue courses was 0.66,
352 0.69, and 1.31, respectively (P=0.010, high-dose group versus vehicle; P=0.055, low-
353 dose versus vehicle). There was no difference in the mean number of ulcer
354 occurrences per month across treatment groups (0.001 for QID, 0.003 for BID;
355 P=0.996 for both versus vehicle). The total number of cases of corneal ulceration
356 was 4 (7.0%) in the high-dose group, 3 (5.6%) in the low-dose group, and 3 (5.2%)
357 in the vehicle group. Both active treatments were generally favored over vehicle in
358 terms of the composite efficacy scores across most subgroups defined by patient
359 Baseline characteristics (**Fig 3**).

360

361 **OTHER EFFICACY ENDPOINTS**

362 The benefits of CsA CE treatment, particularly with the high dose, were evident on
363 most secondary efficacy endpoints. The 4 key VKC symptoms as measured on the
364 VAS improved over time in each treatment group. The greatest symptom
365 improvement was observed in the CsA CE high-dose group, with the largest
366 symptom decrease seen from Baseline to Month 1. CsA CE high-dose provided
367 significantly greater symptom improvement versus vehicle at Months 1, 2, and 4 for
368 photophobia, Months 2 and 4 for tearing, and at all monthly time points for itching
369 and mucous discharge (**Fig 4**). Significant improvements with CsA CE low-dose
370 versus vehicle were primarily noted at Month 2.

371

372 The responder rate was significantly higher in the CsA CE high-dose group (57.1%)
373 and low-dose group (61.1%) versus the vehicle group (34.5%) (P=0.015 and
374 P=0.004, respectively). Monthly use of artificial tears was low in all treatment
375 groups, ranging from 1.8% to 7.1% in the CsA CE high-dose group, 0% to 9.3% in the
376 CsA CE low-dose group, and 3.4% to 19.0% in the vehicle group. QoL, as measured
377 by the Symptoms and Daily Activities domain scores on the QUICK questionnaire,
378 improved from Baseline to Month 4 in all treatment groups. The greatest
379 improvements in both domains were observed in the CsA CE high-dose group, with
380 statistical significance versus vehicle demonstrated at most time points (**Fig 5**). A
381 post hoc analysis at Month 4 also revealed that 8 patients (14.3%) in the high-dose
382 group, 4 (7.4%) in the low-dose group, and 1 (1.7%) of those receiving vehicle alone

383 had a VAS score of 0 for the mean of the 4 symptoms, had not experienced
384 ulceration, and had not used rescue medication in the previous 3 months.
385
386 For the IGEE, the investigators provided a positive global assessment of study
387 treatment in most patients. At Month 4, an IGEE rating of satisfactory or very
388 satisfactory was given for 85.7% of patients in the CsA CE high-dose group, 86.0% of
389 patients in the CsA CE low-dose group, and 68.8% of patients in the vehicle group
390 (P=0.080 for both comparisons of active treatment vs. vehicle).

391
392 On slit lamp examination, there was a shift from Baseline to Month 4 in the
393 proportion of patients with grade 2 or 3 findings to grade 0 or 1 findings for
394 conjunctival erythema/hyperemia, conjunctival discharge, papillae, limbal
395 infiltrates, and conjunctival chemosis in all treatment groups. The assessment of
396 conjunctival erythema/hyperemia showed a statistically significant difference
397 between the active treatments versus vehicle (P=0.017 and P=0.031, respectively);
398 the proportion with grade 2-3 findings decreased from 89.3% at Baseline to 25.0%
399 at Month 4 in the CsA CE high-dose group, from 87.0% to 22.2% in the CsA CE low-
400 dose group, and from 84.5% to 34.5% in the vehicle group.

401

402 **SAFETY**

403 The majority of treatment-emergent adverse events (TEAEs) were mild or moderate
404 in severity. Treatment-related TEAEs were similar in incidence across treatment

405 groups, except for instillation site pain, which occurred at a higher rate in the CsA CE
406 high-dose group (**Table 3**).

407

408 Three patients had serious adverse events (severe ulcerative keratitis and tibia
409 fracture in the CsA CE high-dose group, and a head injury in the CsA CE low-dose
410 group); all were considered unrelated to study treatment. There were no clinically
411 relevant changes in ALT, AST, creatinine, blood pressure, or pulse or respiratory
412 rates over the 4-month treatment period. At Month 4, CsA blood levels were
413 measurable in 14 patients (28.0%) in the CsA CE high-dose group and in 5 patients
414 (10.6%) in the CsA low-dose group. The maximum blood CsA concentration in these
415 groups was 0.670 ng/mL and 0.336 ng/mL, respectively; these amounts are
416 considered to be negligible.

417

418 BCDVA improved over the 4-month treatment period in all treatment groups, most
419 prominently in the high-dose group (mean change from baseline: -0.135 [standard
420 deviation: 0.220]). IOP remained stable in all treatment groups. Other safety
421 parameters did not raise any concerns.

422

423

424

DISCUSSION

425 The results of the double-masked, phase 3 VEKTIS trial demonstrated the efficacy
426 and safety of CsA CE in this study cohort of children and adolescents with severe
427 VKC. The study achieved its primary endpoint, demonstrating the superiority of CsA

428 CE high-dose and CsA CE low-dose over vehicle on the composite efficacy score
429 during the 4-month treatment period (P=0.007 and P=0.010, respectively). The
430 benefit of CsA CE treatment was driven largely by a decrease in the CFS score
431 (reflecting less corneal damage), and to a lesser extent, by a decrease in rescue
432 dexamethasone usage. The secondary efficacy endpoints supported the superiority
433 of CsA CE over vehicle, particularly in the high-dose group, where significant
434 improvements in key VKC symptoms, QoL, and responder rate were evident. Thus,
435 the efficacy of CsA CE in VKC was supported by both objective and subjective
436 improvement.

437

438 The greatest improvement in the composite efficacy score was achieved from
439 Baseline to Month 1, indicating that treatment benefits occurred rapidly. Thereafter,
440 improvements in the CsA CE groups paralleled the improvement noted in the
441 vehicle group, demonstrating that the initial treatment benefit was maintained
442 throughout the 4-month treatment period. Previous VKC studies with other CsA
443 formulations and higher CsA concentrations also showed rapid improvement and
444 sustained benefit with continued treatment, with one study indicating that CsA's
445 beneficial effects were independent of any underlying atopic condition.^{14,25}

446 However, the VEKTIS study is the first to enroll a large number of patients with
447 severe VKC and demonstrate efficacy with respect to measures of VKC signs,
448 symptoms, and QoL; limiting disease progression; and reducing the use of rescue
449 medication (corticosteroids).

450

451 The incidence of corneal ulcers was low in our study, which can be attributed to the
452 anti-inflammatory effects of CsA (eg, reduction of hyperemia and CFS score), as well
453 as the use of rescue medication in the event of disease worsening; in addition, the
454 CE vehicle itself has been shown to have beneficial aspects on keratitis, which may
455 explain the lack of a significant difference between the CsA CE and vehicle groups
456 with respect to ulcer formation. Improvements seen in the vehicle group--not only
457 in term of ulceration, but other VKC measures as well--likely reflect a beneficial
458 lubricating effect consistent with the known symptomatic benefits of artificial tears
459 in VKC,^{4,10} as well as changes in VKC severity during the allergy season. The CsA CE
460 formulation used herein was specifically formulated to enhance CsA bioavailability
461 in the eye and was associated with negligible systemic CsA exposure. Consistent
462 with this negligible exposure, there were no clinically relevant changes in ALT, AST,
463 or creatinine over the 4-month treatment period.

464

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

471

472 One limitation of our study was that we only enrolled patients with severe VKC, as it
473 was considered more appropriate to evaluate CsA CE in this population rather than

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

497

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

509

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518

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- 591

592 **FIGURE LEGENDS**

593

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

602

603 **Figure 2.** (A) Mean composite efficacy score at each visit; (B) mean composite
604 efficacy score over the 4-month treatment period. The composite score at each
605 monthly visit was calculated as the difference in corneal fluorescein staining (CFS)
606 score from Baseline, with penalties of -1 for each course of rescue medication or
607 occurrence of corneal ulceration; a positive value indicated improvement. BID, twice
608 daily; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); LS, least-squares;
609 SEM, standard error of the mean; QID, four times daily.

610

611 **Figure 3.** Forest plot of (A) high-dose CsA CE (QID) and (B) low-dose CsA CE (BID)
612 versus vehicle alone for the composite efficacy score in key subgroups. The
613 composite score at each monthly visit was calculated as the difference in CFS score
614 from Baseline, with penalties of -1 for each course of rescue medication or
615 occurrence of corneal ulceration; a positive value indicated improvement. BID, twice

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

619

620 **Figure 4.** Improvement on the VAS (0-100 mm) for the symptoms of (A)
621 photophobia and tearing and (B) itching and mucous discharge. A decrease in VAS
622 score from Baseline indicates improvement. P-values were derived via LMMRM with
623 adjustment through the Hochberg's procedure. BID, twice daily; CI, confidence
624 interval; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); LS, least-
625 squares; LMMRM, linear mixed model for repeated measures; QID, four times daily;
626 SEM, standard error of the mean; VAS, visual analogue scale.

627

628 **Figure 5.** Improvement in quality of life (QoL) on the QUICK questionnaire (A)
629 Symptoms domain and (B) Daily Activities domain. Minimum QoL score is defined
630 as 0 (positive) and maximum is 100 (negative). P-values were derived via LMMRM
631 with adjustment through the Hochberg's procedure. BID, twice daily; CI, confidence
632 interval; CsA CE, cyclosporine A cationic emulsion 0.1% (1 mg/mL); LMMRM, linear
633 mixed model for repeated measures; LS, least-squares; QID, four times daily; QUICK,
634 Quality of Life in Children with Vernal Keratoconjunctivitis.

635

Fig. 1

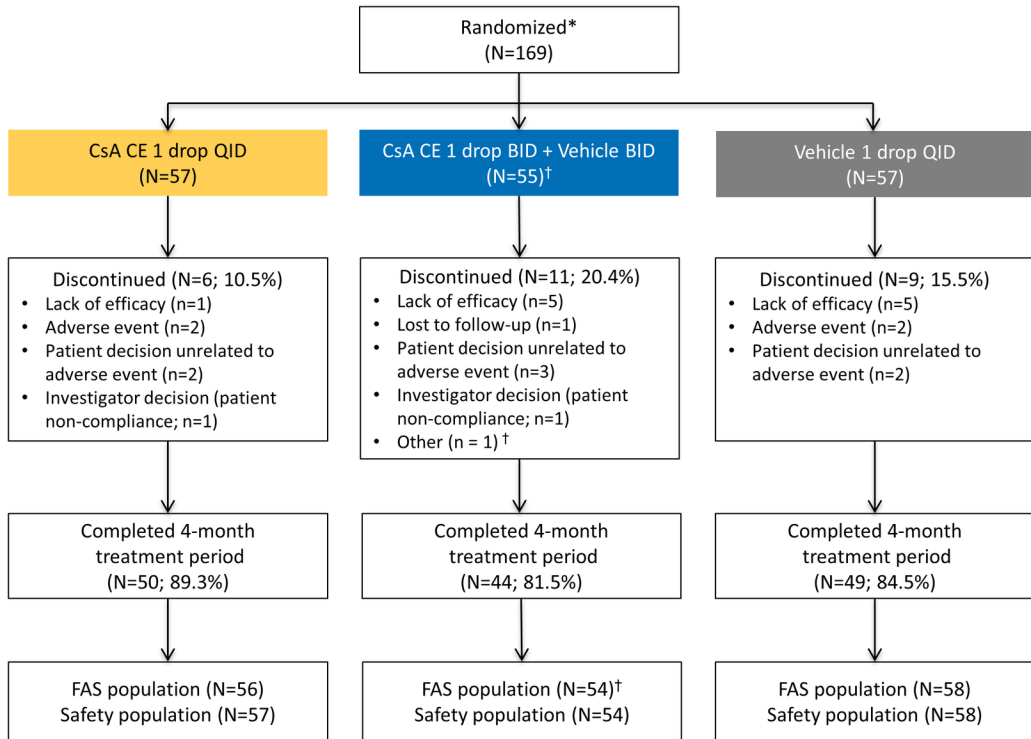


Fig. 2A

A.

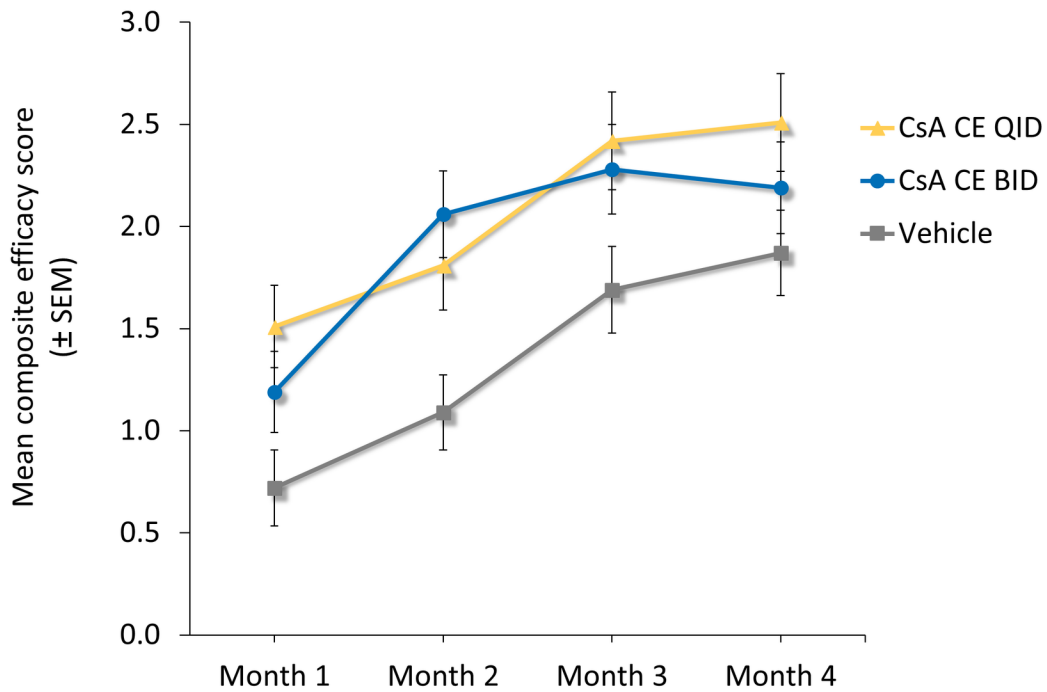


Fig. 2B

B.

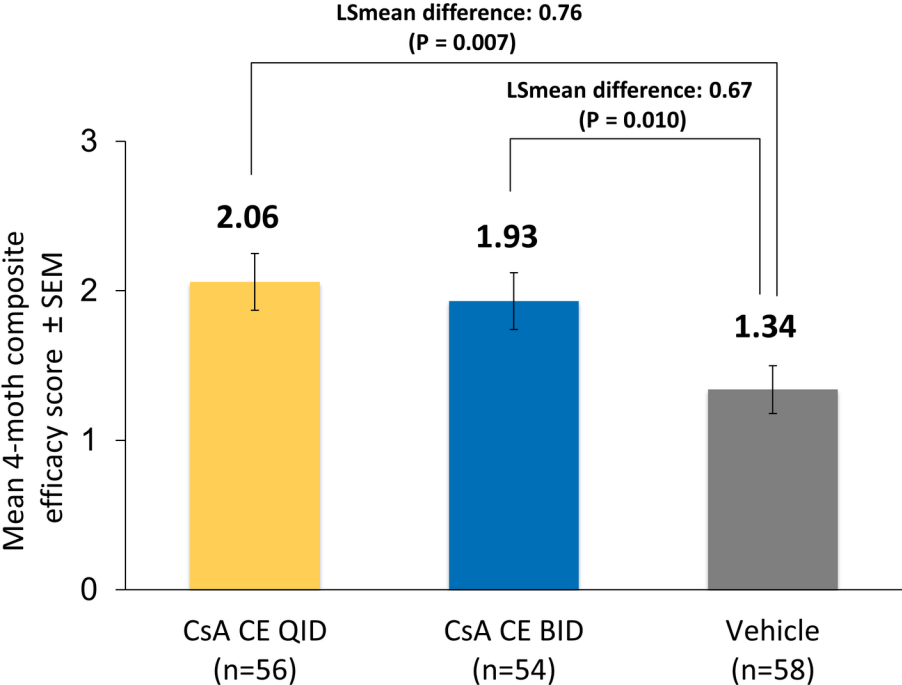


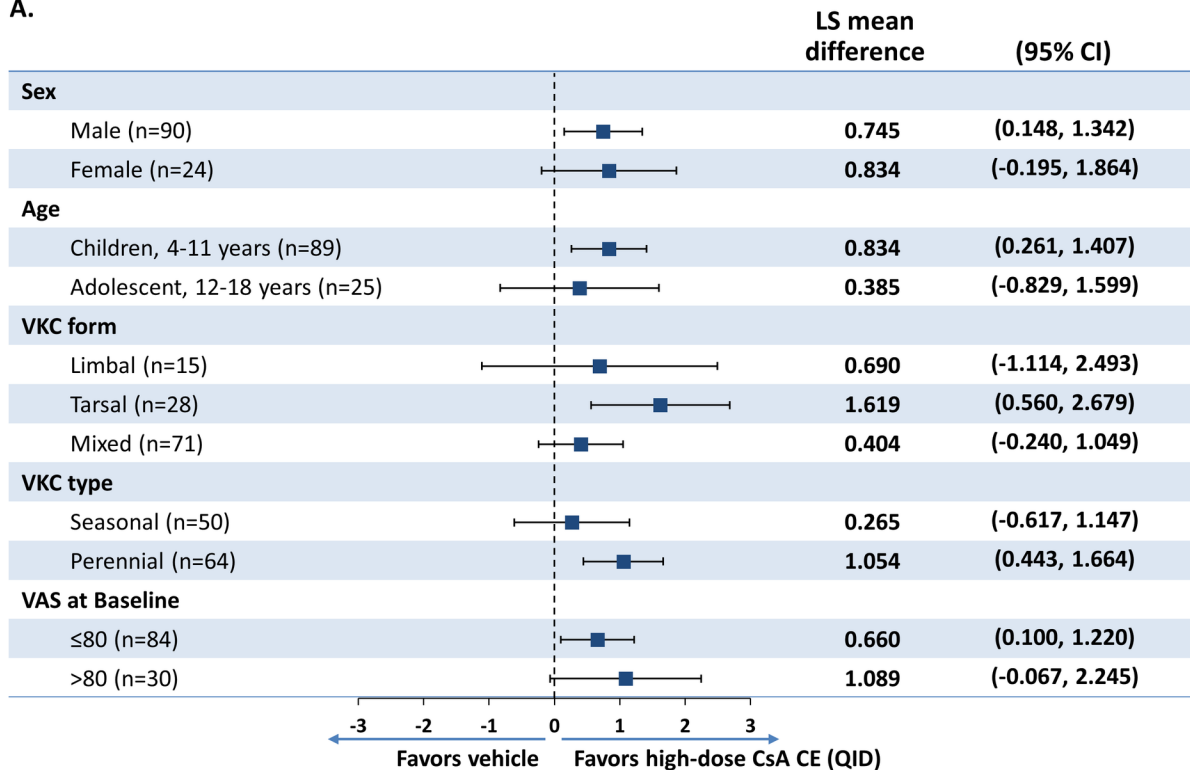
Fig. 3A**A.**

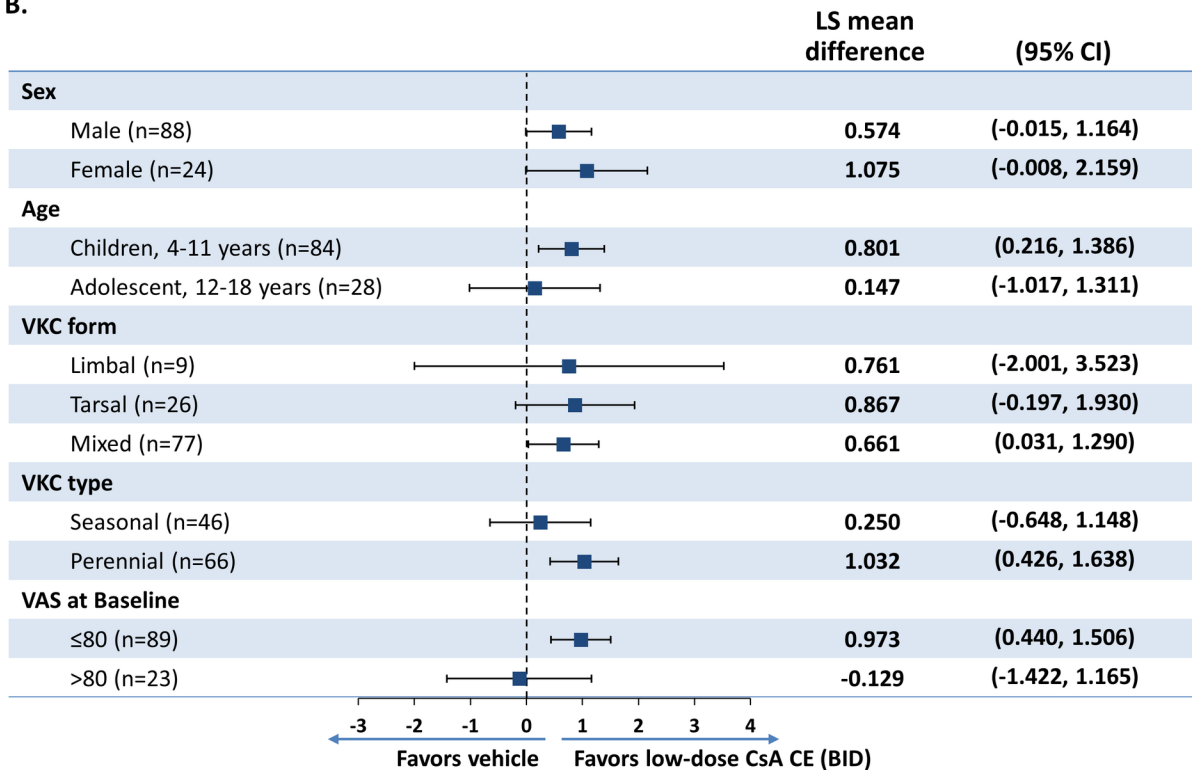
Fig. 3B**B.**

Fig. 4A

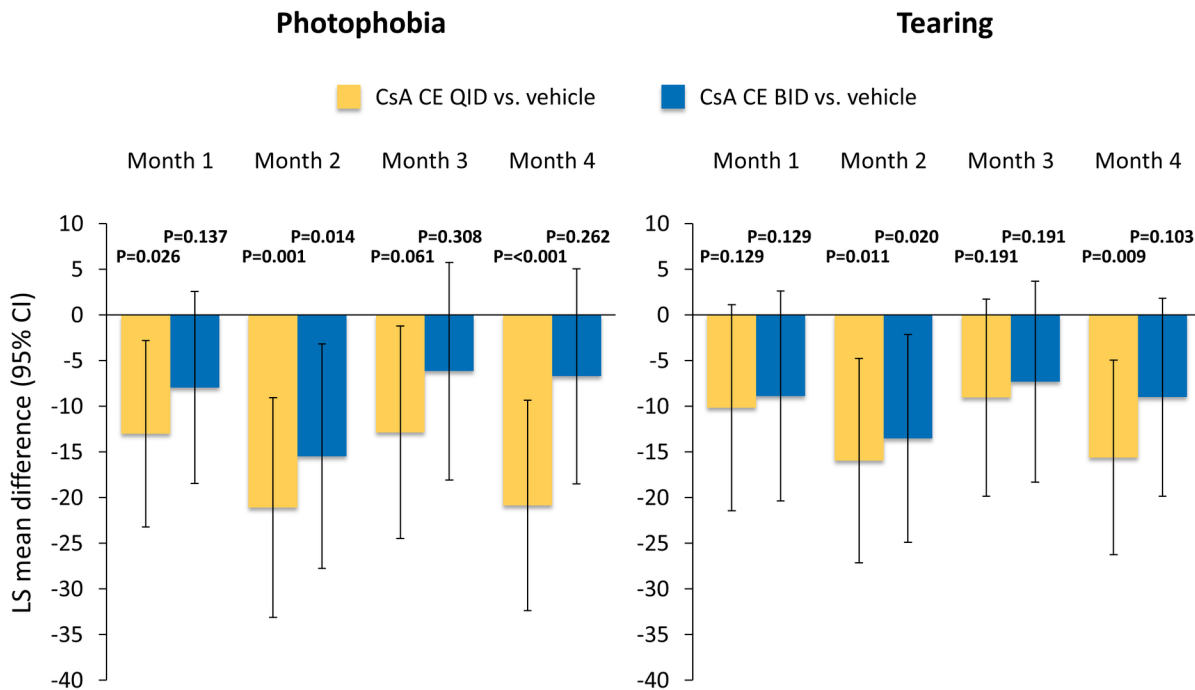


Fig. 4B

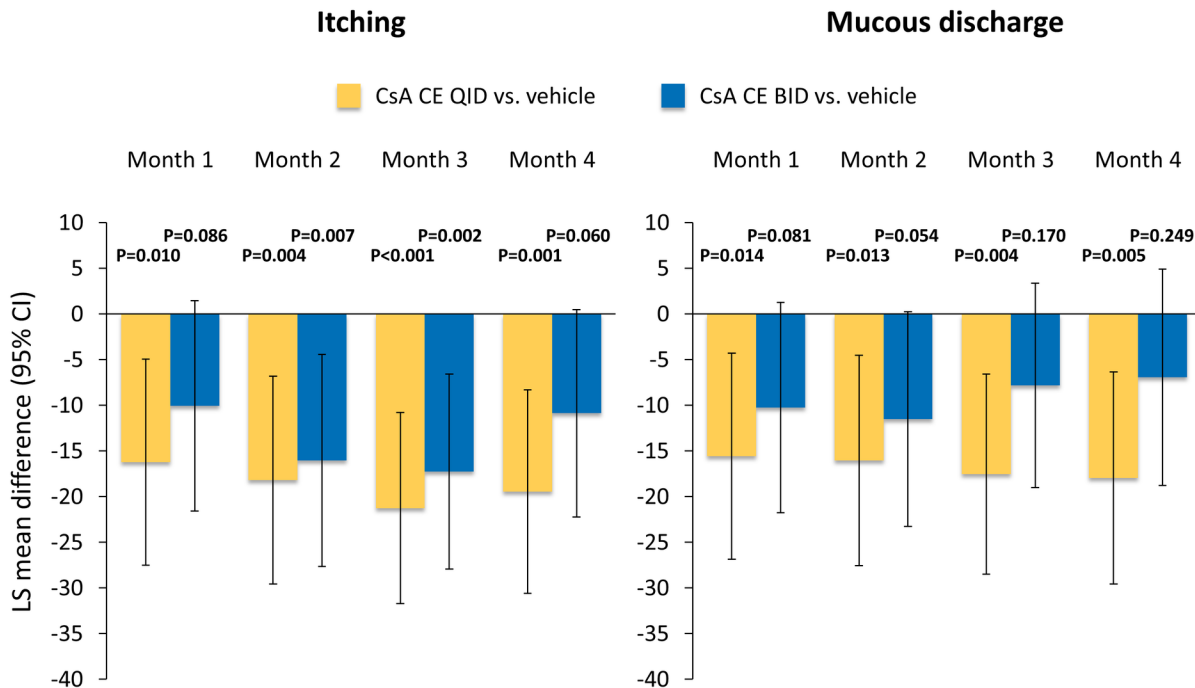


Fig. 5A

A. Symptoms

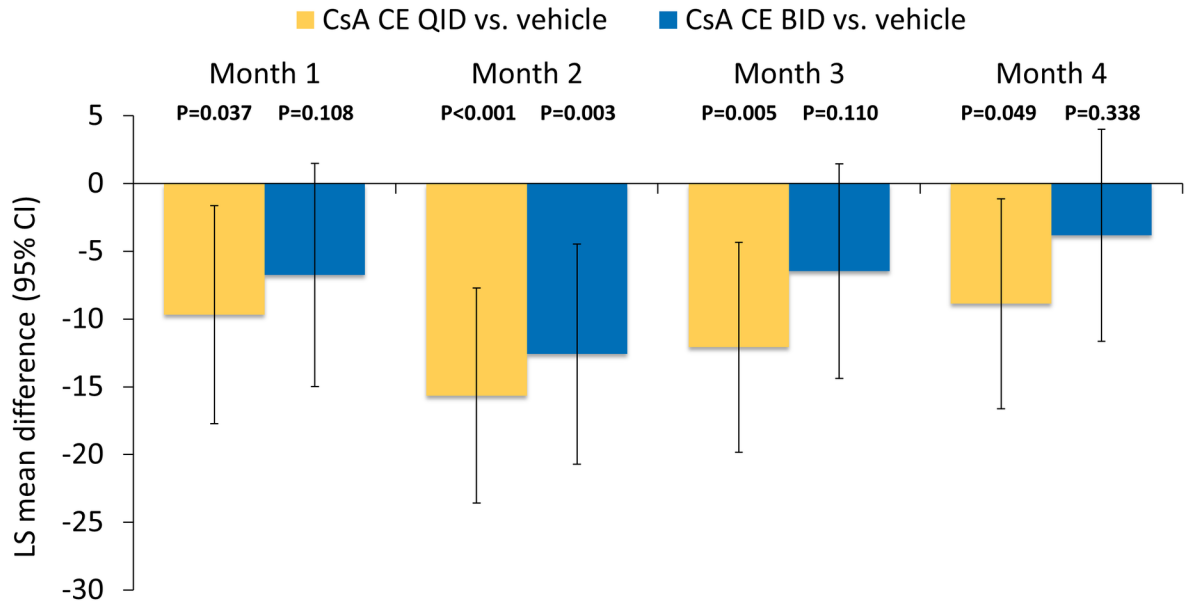


Fig. 5B

B. Daily activities

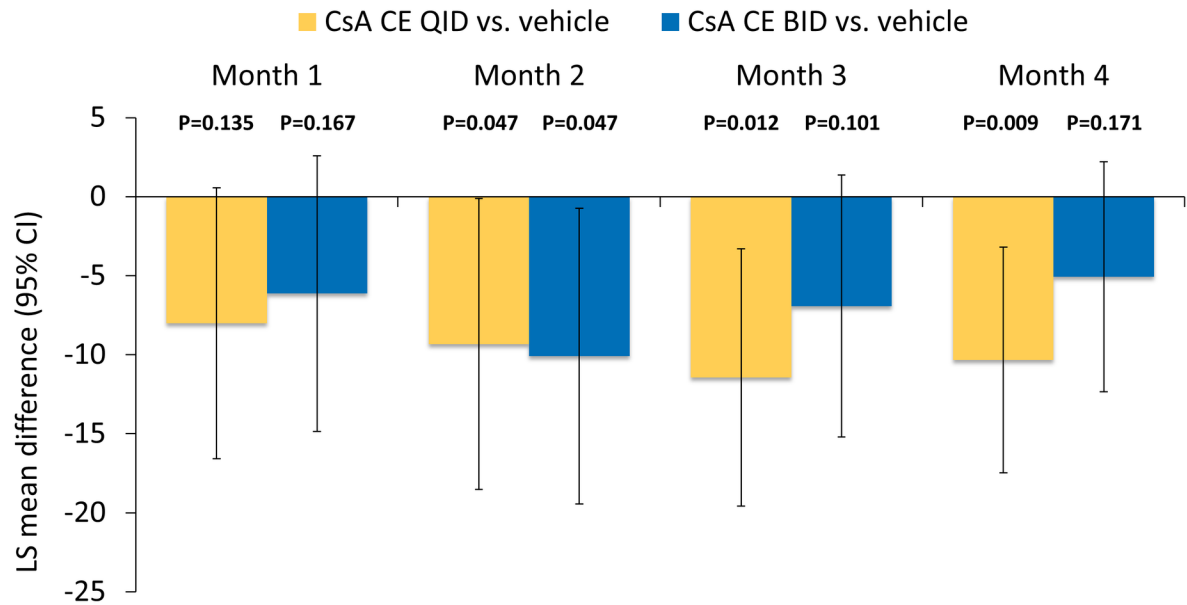


Table 1. Demographic and Baseline Characteristics of the FAS Cohort

Characteristic	CsA CE	CsA CE	Vehicle
	QID (N=56)	BID (N=54)	
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	CsA CE	Vehicle
	QID (N=57)	BID (N=54)	
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.