A Water-free 0.1% Cyclosporine A Solution for Treatment of Dry Eye Disease: Results of the Randomized Phase 2B/3 ESSENCE Study

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Purpose: To assess the efficacy, safety, and tolerability of a topical water-free cyclosporine A formulation (CyclASol 0.1% ophthalmic solution) in comparison with vehicle for the treatment of dry eye disease (DED).

Methods: Three hundred twenty-eight patients were enrolled in this prospective, 12-week, multicenter, randomized, double-masked, confirmatory, vehicle-controlled clinical study. After a 2-week run-in period, eligible DED patients were randomized 1:1 to either CyclASol 0.1% or vehicle twice daily. The primary efficacy endpoint was change from baseline in total corneal fluorescein staining (National Eye Institute scale), and the second hierarchical primary efficacy endpoint was change from baseline in the Ocular Surface Disease Index score, both at 4 weeks. Secondary efficacy and safety assessments included conjunctival lissamine green staining (Oxford scale), visual analog scales for dry eye symptoms, and adverse event.

Results: Treatment with CyclASol 0.1% was superior to vehicle in the primary endpoint: total corneal fluorescein staining at week 4 (Δ −0.8; 95% confidence interval, −1.3 to −0.4; $P = 0.0002$, analysis of covariance). This difference had already reached statistical significance after 2 weeks and was maintained throughout the study. The study did not statistically meet its second hierarchically tested primary endpoint: Ocular Surface Disease Index score ($P = 0.2634$). However, CyclASol 0.1% treatment showed statistically significant improvement compared with that of vehicle in the eye dryness score at week 4 (Δ −4.783; 95% confidence interval, −9.129 to −0.438; $P = 0.0311$).

Conclusions: CyclASol 0.1% was effective in treating signs and symptoms of DED. It significantly reduced corneal and conjunctival staining and improved ocular dryness compared with vehicle. CyclASol 0.1% was safe and showed excellent tolerability.

Key Words: DED, cyclosporine, semi-fluorinated alkane, corneal staining, conjunctival staining, dryness score, visual function

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INTRODUCTION

Dry eye disease (DED) is defined by the International Dry Eye Workshop (TFOS DEWS II) as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1] In DED patients, activities requiring prolonged gazing with involuntary suppression of blinking can lead to ocular surface irregularities and corneal epithelium damage,[2] both affecting visual function[3] and eventually preventing patients from performing basic activities of daily life such as reading, driving, or working with screens.[4] Consequently, DED negatively impacts quality of life comparable with other severe diseases.[5] Recently, the impact of DED on reading speed has been increasingly investigated,[6–11] suggesting that reading speed might be substantially affected by the level of corneal staining, especially under straining conditions in daily life such as prolonged duration of reading.

The treatment under investigation, CyclASol 0.1%, is a clear topical water-free ophthalmic solution of cyclosporine A in a novel vehicle, the semifluorinated alkane (SFA)-based EyeSol technology, using the SFA perfluorobutylpentane (abbreviated F4H5). This topical formulation was developed for the treatment of DED with the goal of increasing local

bioavailability, avoiding the use of oils, surfactants, and preservatives. Cyclosporine A is an antiinflammatory agent with immunomodulatory properties with proven efficacy in DED.[12] Potential benefits of the CyclASol 0.1% formulation in a water-free SFA solution include improved tolerability and decreased visual disturbance compared with typical cyclosporine A formulations, which frequently involve surfactants and oils. A further potential benefit is an improved clinical efficacy because of better local bioavailability. CyclASol has been investigated previously in one phase 1 clinical study with healthy volunteers and one phase 2 clinical study in patients with DED. Both clinical studies showed an excellent tolerability and safety profile. The CyclASol phase 2 study was a randomized, double-masked, vehicle-controlled, dose finding study with CyclASol 0.05% and CyclASol 0.1% and an open-label active comparator and showed a consistent reduction in corneal and conjunctival staining after treatment with CyclASol compared with the vehicle and with the active comparator, with an early onset of effect as of week 2.[13] The central area of the cornea, which is an important region relevant to visual function, benefitted most. Thus, reading assessments were included in the present phase 2B/3 study. The treatment effect on cornea staining parameters was more pronounced in patients with higher baseline values of total corneal fluorescein staining (CFS). Therefore, patients with total CFS scores ≥10 [National Eye Institute (NEI) scale] at baseline were chosen for the confirmatory clinical phase 2B/3 study. The 0.1% concentration was selected for its trend toward a better effect on symptoms in the target population. This work presents the results of the phase 2B/3 study CYS-003 (ESSENCE) designed to confirm the efficacy, safety, and tolerability of CyclASol 0.1% ophthalmic solution in comparison with its vehicle (F4H5) for the treatment of signs and symptoms of DED.

METHODS

Study Design

A phase 2B/3, multicenter, randomized, prospective, double-masked study was performed to evaluate the efficacy, safety, and tolerability of CyclASol 0.1% ophthalmic solution in comparison with its vehicle in patients with predominantly aqueous deficient DED, not responding to treatment with artificial tears. The study was performed at 9 investigational clinical sites in the United States after review and approval by the institutional review board, Alpha Institutional Review Board, San Clemente, CA. It was performed in accordance with the Health Insurance Portability and Accountability Act of 1996, the Declaration of Helsinki, the protocol, the International Conference on Harmonization guideline on Good Clinical Practices, and all other applicable local regulatory requirements and laws. The study was registered at www.clinicaltrials.gov (NCT03292809).

After informed consent was obtained, patients who met all eligibility requirements started with an open-label 2-week run-in period using Systane Balance (Alcon Laboratories, Inc, Fort Worth, TX) lubrication eye drops twice a day (BID). Thereafter, patients returned and, on confirma-

tion of the study eligibility criteria, randomized at day 1 to 1 of the 2 treatment arms, CyclASol 0.1% or vehicle, in a 1:1 ratio by using the Interactive Web Response System. Randomization was stratified on clinical site and total Ocular Surface Disease Index (OSDI) score. During the treatment period, patients dosed a single drop per eye BID for 12 weeks (Fig. 1). Investigators, study staff, and patients were all masked to study treatment. All treatment arms used identical multidose bottles, fill volumes, and labels. No patient was unmasked during the study. No other drops were permitted.

Patients

A total of 727 patients aged at least 18 years, with a history of DED in both eyes were screened at the 9 selected investigational sites. Patients were enrolled into the study if 1 eye (the same eye) met the following main inclusion criteria at both screening and at time of randomization: total CFS ≥10 (NEI scale), total OSDI score ≥20, total conjunctival staining score ≥2 (Oxford scale and lissamine green), and Schirmer test I (without anesthesia) between ≥1 and ≤10 mm. Patients were excluded from participating if clinically relevant abnormal slit lamp findings or lid anatomy were observed at screening, including trauma, Stevens–Johnson syndrome, active blepharitis, meibomian gland dysfunction or lid margin inflammation, DED secondary to scarring, ocular or periocular malignancy, intraocular surgery or ocular laser surgery within the previous 6 months, active ocular allergies, use of contact lenses within 3 months before screening, ongoing ocular or systemic infection, history of herpetic keratitis, or use of topical cyclosporine A within 2 months before screening.

Assessments of Outcome Measures

Signs and symptoms of dry eye, in addition to clinical safety parameters were assessed for both eyes at screening (−2 weeks), baseline (day 1), and again during the 4 follow-up visits during the treatment period [week 2, week 4 (day 29), week 8, and week 12]. Treatment compliance was assessed using a diary.

Efficacy endpoints were measured using total and subregion CFS (NEI scale) and OSDI questionnaire. CFS was assessed in each eye using the NEI scale, which ranges from 0 to 3 for each of the 5 areas of the cornea. Higher values describe greater staining and corneal damage. The

FIGURE 1. Study design. Eligible patients entered at visit 0 a 2-week run-in phase with Systane Balance and were randomized at visit 1 to the CyclASol 0.1% or vehicle group (1:1). Primary analysis took place at visit 3 (day 29 = week 4), and the study was continued until week 12. (The full color version of this figure is available at www.corneajrnl.com.)

OSDI score is a composite measure built on 12 questions, with totals ranging from 0 to 100, and higher scores representing a worse disease index. Conjunctival staining (Oxford scale) was measured using lissamine green dye, the scale ranging from 0 to 5 for nasal and temporal regions, with higher scores representing greater conjunctival damage. Visual analog scale is a subject-reported symptom index (0–100 scale; 0 = no discomfort, 100 = maximal discomfort) including "eye dryness score," burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, awareness of symptoms, and frequency of dryness. A series of 5 English language reading tests (silent reading; IReST[14] at normal print size, at low contrast, and critical print size; and the Wilkins test) were performed to assess reading speed in words per minute (wpm) while using a tablet device at baseline, week 4, and week 12. Additional prespecified efficacy measures included Schirmer test I, tear film break-up time, worst symptom selection and assessment, Reading Impairment Score, matrix metallopeptidase 9 (InflammaDry; Quidel, San Diego, CA), Ocular Discomfort and 4-Sympom Questionnaire (Ora Calibra scale), and dry eye symptoms as recorded in a diary.

Ocular signs were analyzed by "study eye," which was the eye with the highest CFS score (NEI scale) at baseline. If the total CFS score at baseline was the same in both qualifying eyes, then the right eye was designated as the study eye. Ocular symptoms were assessed per patient, thus for both eyes simultaneously.

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) occurring after the first dose of randomized study treatment was administered or if an AE worsened in severity or increased in frequency after the first dose of randomized study treatment. The investigator determined severity and relationship to the study treatment. All AEs were coded using the Medical Dictionary for Regulatory Activities version 20.1.

Statistical Methods

This study was expected to enroll 158 patients in each of the 2 treatment arms. A true difference of −0.85 was assumed for the mean change from baseline (CFB) in total CFS (NEI scale) at week 4 with a common of 2.2. For the mean CFB in total OSDI score, a true difference of −5.0 was assumed, with a common SD of 14.5. A sample size of 142 patients per group would lead to 90% power to reject the null hypothesis for the primary sign endpoint (total CFS) and 82% power to reject the null hypothesis for the primary symptom endpoint (total OSDI score) and show a significant difference at the 2-sided α = 0.05 level. Accounting for patient discontinuations, 316 total enrolled patients were planned, assuming a dropout rate of 10%. Hierarchical testing was selected to protect the α error with total CFS being tested first.

The primary efficacy analysis was performed on the study eye of the full analysis set, which included all randomized patients having received at least 1 dose of study treatment. These patients were analyzed as randomized using observed data only.

The primary efficacy analyses compared the mean CFB in total CFS score (NEI scale) and in total OSDI score and were analyzed separately using an analysis of covariance (ANCOVA) model with terms for patient baseline value, site, treatment, and the interaction of treatment by baseline value. Secondary variables were analyzed using an ANCOVA model adjusted for baseline value and site. Least squares means for each treatment group and for the difference between treatment groups were presented from the model together with 2-sided *P* values and 95% confidence intervals (CIs).

RESULTS

Subject Disposition

The first patient was screened on October 19, 2017, and the last patient completed the study on May 22, 2018. Of 727 patients screened, 328 patients were enrolled at visit 1, randomizing 162 patients to the CyclASol 0.1% group and 166 patients to the vehicle group. A total of 95.7% patients in the CyclASol 0.1% group and 98.2% in the vehicle group completed the study (Fig. 2).

Baseline Characteristics

The patients' demographic characteristics of age, sex, and disease duration were well balanced between the treatment groups (Table 1). The baseline disease characteristics were comparable between the 2 treatment groups. The patient population was characterized by significant corneal surface staining with a mean total CFS score of 11.5 (of 15), a
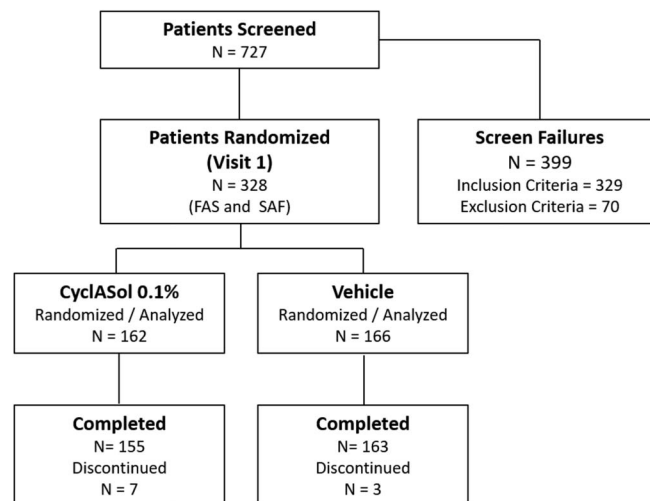
FIGURE 2. Patient flow. Of 727 screened patients at visit 0, 328 patients were randomized to either CyclASol 0.1% (N = 162) or vehicle (N = 166) treatment. In the CyclASol 0.1% group, 3 patients discontinued due to patient choice, 2 patients discontinued due to AEs, and 2 patients discontinued due to administrative reasons. In the vehicle group, 2 patients discontinued due to administrative reasons, and 1 patient discontinued due to medical monitor/investigator discretion. FAS, full analysis set. SAF, safety analysis set.

TABLE 1. Demographics

	CyclASol 0.1% (N = 162)	Vehicle (N = 166)	All Subjects (N = 328)
Age (yr)			
Mean (SD)	61.5 (13.60)	61.3 (12.66)	61.4 (13.11)
Minimum, maximum	18, 93	19, 89	18, 93
Sex			
Male, n (%)	46 (28.4)	47 (28.3)	93 (28.4)
Female, n (%)	116 (71.6)	119 (71.7)	235 (71.6)
Disease duration (yr)			
Mean (SD)	12.17 (10.595)	12.34 (10.693)	12.26 (10.629)
<10-yr duration, n (%)	81 (50.0)	80 (48.2)	161 (49.1)
≥10-yr duration, n (%)	81 (50.0)	86 (51.8)	167 (50.9)

N, number of subjects enrolled in each respective treatment group within the safety population; %, based on the total number of subjects in each treatment group.

mean central CFS score of 2.0 (of 3.0), and a Schirmer test I mean value of approximately 5 mm (Table 2) at baseline.

Efficacy
Signs

The primary analysis (ANCOVA) showed that improvement from baseline in mean total CFS was statistically significantly greater in the CyclASol 0.1% group than that in the vehicle group (Δ −0.8; 95% CI, −1.3 to −0.4; P = 0.0002) (Fig. 3). The primary sign endpoint was met, and the study demonstrated superiority of CyclASol 0.1% over vehicle in mean CFB in total CFS score. Secondary analyses demonstrated that reduction in total corneal staining was statistically significantly superior in the CyclASol 0.1% group compared with that in the vehicle throughout the study (week 2–week 12) (Fig. 3).

A similar pattern was observed for central CFS with early onset of effect at week 2 and maintenance of this effect throughout the study (data on file). Conjunctival lissamine green staining also demonstrated reductions over time, becoming statistically significant at the earliest visit (week 4, data on file), favoring CyclASol 0.1% group over vehicle group (conjunctival staining: Δ −0.6; 95% CI, −0.9 to −0.3; P = 0.0003, respectively).

Symptoms

Both the CyclASol 0.1% and vehicle groups showed statistically significant decreases from baseline at week 4 in total OSDI score. This improvement in total OSDI score of the CyclASol 0.1% group did not reach statistical significance compared with that of the vehicle group (P = 0.2634) at week 4 in the primary analysis for this hierarchically tested endpoint.

The mean CFB for the secondary endpoints eye dryness score and frequency of dryness showed statistically significant decreases for CyclASol 0.1% compared with those for vehicle at the primary endpoint visit (at week 4 for eye dryness score: Δ −4.88; 95% CI, −9.13 to −0.44; P = 0.0311, and for frequency: Δ −5.32; 95% CI, −10.23 to −0.41; P = 0.034, respectively). In addition, differences in

mean CFB in other symptoms, awareness of dryness and blurred vision, were observed to favor CyclASol, without achieving statistical significance (P = 0.053 and 0.102, respectively) (Fig. 4).

Post Hoc Analysis

Additional subgroup analyses were performed to determine the magnitude of CyclASol 0.1% effect on signs and symptoms in different subgroups compared with the overall group. Patients with higher symptomatology at baseline (eye dryness score ≥50 and ≥70), still representing most study patients, showed consistently larger treatment effects for dryness-related symptoms compared with the overall population. Importantly, the effect on signs (total and central fluorescein staining scores) in this subpopulation is comparable with the overall population.

Patients in the CyclASol 0.1% group across all post-baseline assessments were consistently more likely to demonstrate a response to treatment in the study eye, with a reduction in total CFS score of ≥3, in central fluorescein staining score of ≥1, and in total conjunctival lissamine green staining score of ≥2. These treatment-response rates in the CyclASol 0.1% group were high with >50% responders for both total and central fluorescein staining scores from week 4 onward and were statistically significantly higher for CyclASol 0.1% than vehicle at week 4 [total fluorescein staining responder 52.9% vs 40.6%; P = 0.0337 (Fisher test)] (Fig. 5).

Additional Efficacy Endpoints
Reading Speed

The reading tests under challenged conditions (IReST at low contrast and critical print size) showed statistically significant increases in reading speed over the course of the study for both treatments. For the critical print size IReST, the improvement was 10 wpm (baseline: 120 wpm) and 8 wpm (baseline: 124 wpm) in the CyclASol and vehicle groups, respectively. These improvements were mirrored by the

TABLE 2. Baseline Disease Characteristics

	CyclASol 0.1% (N = 162), Mean (SD)	Vehicle (N = 166), Mean (SD)
Total CFS	11.5 (1.26)	11.5 (1.25)
Central CFS	2.0 (0.51)	2.0 (0.52)
Dryness score	68.5 (21.64)	69.9 (20.45)
Total OSDI score	46.9 (16.73)	47.1 (16.41)
Reading impairment score	2.1 (1.13)	2.1 (1.02)
Unanesthetized Schirmer test (mm)	5.2 (2.83)	5.1 (2.64)
Total lissamine green conjunctival staining	4.2 (1.64)	4.4 (1.73)
Best-spectacle corrected visual acuity (logMAR)	0.120 (0.1482)	0.116 (0.1409)
Matrix metallopeptidase 9 positive, N (%)	71 (43.8)	72 (43.4)

N, number of subjects enrolled in each respective treatment group within the safety population; %, based on the total number of subjects in each treatment group.
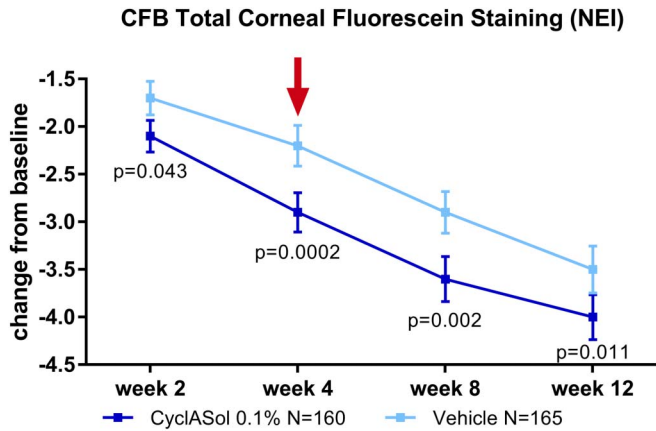
CFB Total Corneal Fluorescein Staining (NEI)

FIGURE 3. Mean CFB for total CFS over the treatment period for worst eye in the full analysis set population. Statistically significant versus vehicle ($P \le 0.0002$) at week 4 and for all other tested timepoints (week 2, 8, 12) in ANCOVA. Error bars show SEM. The NEI scale divides the cornea into 5 regions. The total score is the sum of all regions (0–3 per region, total score of 15 indicates maximum staining). (The full color version of this figure is available at www.corneajrnl.com.)

patients' self-reported reading impairment score, which also decreased, reflecting that patients experienced overall less problems with reading during treatment. Given that the reading speed improvements were not statistically significantly different between the treatment groups, we conducted an analysis irrespective of treatment, addressing how subjects with larger improvements in corneal staining [eg, >3 grades (defined as responder)] compared with those who do not have such a response (defined as nonresponder) to show that individual improvements in this order of magnitude are relevant for visual function. Indeed, responders showed a statistically significant ($P = 0.049$) difference in critical print size reading speed compared with patients with less or no improvement in total CFS scores (nonresponders). Compared with baseline, the difference in the responder group was about 13 wpm and highly statistically significant ($P = 0.0009$), whereas the nonresponder improved by 3 wpm, a difference that was not statistically significant (Fig. 6).

Tear Production

The proportion of patients having an improvement in Schirmer test I results of >10 mm compared with that of baseline was higher in the CyclASol 0.1% group compared with that of the vehicle group throughout the study. This difference approached significance at week 2 and week 12 (Fisher exact test: $P = 0.0844$ and $P = 0.0690$, respectively).

Safety

Ninety of the 328 randomized patients (27.4%) reported 143 TEAEs during the study period. The number of patients reporting at least 1 TEAE or ocular TEAE were in the same order of magnitude for the CyclASol 0.1% group compared with that of the vehicle group (20.4% and 20.5% or 12.3% and 8.4% in the CyclASol 0.1% group and vehicle group,

respectively). The most common ocular TEAEs were reduced visual acuity, vision blurred, and instillation site pain (Table 3). Most TEAEs reported in the study were of mild to moderate intensity, with 1 patient in the vehicle group reporting a nonocular TEAE of severe intensity (Table 3). Three patients withdrew from study treatment due to TEAE, which were ocular and occurred in the CyclASol 0.1% group. Two of them, foreign body sensation and eyelid edema, were suspected to be related to study treatment and had recovered by the end of the study. The third event of ocular discomfort was not suspected to be related to study treatment and had not recovered by the end of the study. No deaths were reported in the study. Three serious TEAEs (small intestinal obstruction, pneumonia, and intervertebral disc degeneration) were reported during the study by patients in the vehicle group, none of which were considered related to study treatment.

Across all treatment groups, no significant changes from baseline were observed by slit lamp biomicroscopy, dilated fundoscopy, or in mean visual acuity or intraocular pressure. Mean drop comfort scores for both groups were very low, ranging between 1 and 2 in the study eye, fellow eye, or in all qualified eyes. There was no statistically significant difference in drop comfort score on instillation between the treatment and vehicle groups ($P = 0.2255$).

DISCUSSION

This first confirmatory phase 2B/3 clinical study (CYS-003, ESSENCE) evaluated efficacy, safety, and tolerability of CyclASol, a SFA-based water-free 0.1% cyclosporine A eye drop formulation, for the treatment of signs and symptoms of DED compared with its vehicle (F4H5), when administered topically BID for 12 weeks. As intended and defined in the patient eligibility criteria, the study population is reflective of patients with predominantly aqueous deficient DED characterized by low Schirmer I test values and significant ocular
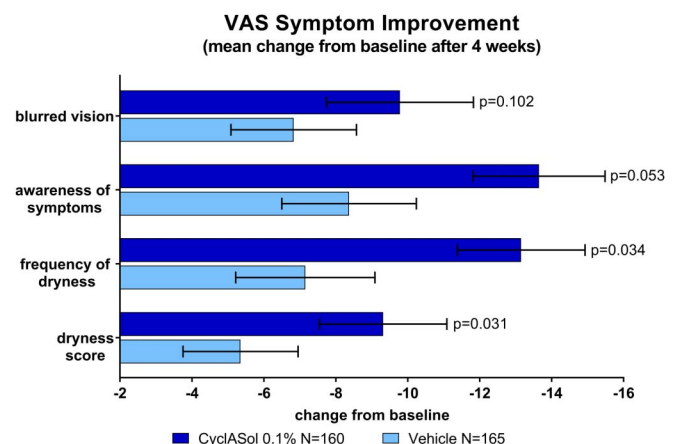
VAS Symptom Improvement
(mean change from baseline after 4 weeks)

FIGURE 4. Mean CFB for visual analog scale (VAS) symptoms at week 4. Improvements were statistically significantly different in CyclASol 0.1% versus vehicle for dryness score and frequency of dryness ($P = 0.031$ and $P = 0.034$, respectively) in ANCOVA. Error bars show SEM. The VAS grading scale ranges from 0 to 100. (The full color version of this figure is available at www.corneajrnl.com.)
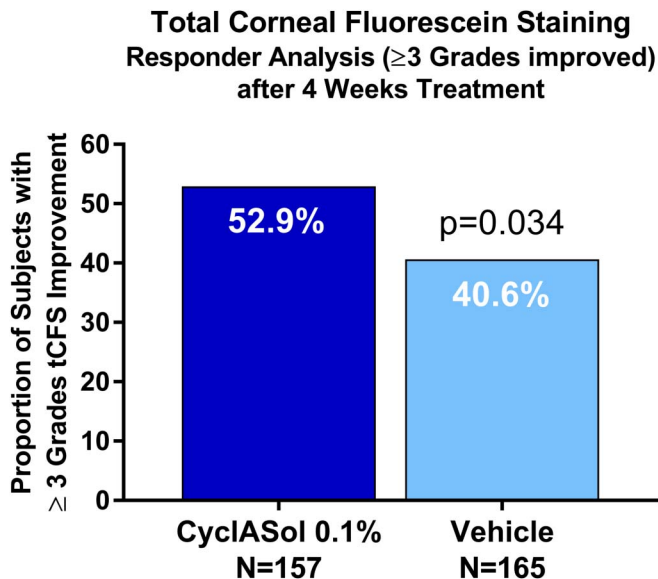
Total Corneal Fluorescein Staining
Responder Analysis (≥3 Grades improved) after 4 Weeks Treatment

FIGURE 5. Total CFS responder are defined by an improvement (decrease) of greater or equal to 3 grades (NEI scale) at week 4 compared with baseline. The difference was statistically significantly different between the groups favoring CyclASol 0.1% (*P* = 0.034). (The full color version of this figure is available at www.corneajrnl.com.)

surface damage at baseline. Despite normal best-spectacle corrected visual acuity, these patients reported, on average, having significant reading problems half of their time, which could be likely attributed to their DED and corneal staining. This study met its primary sign endpoint; it demonstrated superiority of CyclASol 0.1% in reducing ocular surface epithelial lesions (total CFS) compared with vehicle at week 4. This healing effect on the ocular surface started early (week 2) and was persistent over the duration of the 12-week study. Statistically significant improvements in total and central CFS starting at week 2 and conjunctival staining at the earliest assessment of the parameter (week 4) were consistent with the results of the previous phase 2 study,[13] which also showed an early onset of treatment effect in total and central CFS at week 2 and becoming statistically significant at week 4. This onset of action is earlier than reported with other cyclosporine A products[15–17] and very likely a result of the novel water-free formulation. For example, a statistically significant effect on corneal staining after 4 months of treatment was found with 0.05% cyclosporine A emulsion.[15] With 0.1% cationic emulsion a statistically significant effect on corneal staining was observed after 3 months,[16] and for cyclosporine A containing nanoemulsion, a statistically significant effect on corneal staining was reported as early as 4 weeks and on conjunctival staining after 8 weeks.[17] It is believed that the onset of effect of cyclosporine A might take months because of its effect on T-cells, which depends on T-cell turnover rate. However, cyclosporine A also possesses immediate T-cell independent antiinflammatory mechanisms such as inhibition of apoptosis in conjunctival cells and induction of T cell apoptosis and NFkB inhibition.[18–20] These immediate effects

in combination with the enhanced local bioavailability using the novel water-free carrier and absence of ocular surface harming ingredients contribute to CyclASol's early onset of effect in comparison with other cyclosporine A containing products.

Although the second hierarchically tested symptom endpoint (OSDI) was not met statistically (*P* = 0.2634), several prespecified secondary visual analog scale scored symptom endpoints [eye dryness score (*P* = 0.0311); frequency of dryness (*P* = 0.0338)] were statistically better compared with those of the vehicle group. This, efficacy on both sign and symptom endpoints in the same clinical DED study at the same observation time, is a remarkable finding.[21] More so in view of the historical challenges of clinical studies in DED showing discordance in both severity and magnitude of treatment effects on signs and symptoms in seemingly identical DED study populations.[22] Furthermore, the chosen assessment tool for symptoms plays an important role. Although OSDI is a composite endpoint in which the overall score is calculated from various symptom scores, the eye dryness score focuses on a single leading symptom. Dryness and discomfort are symptoms that have been consistently scored highest in DED questionnaires,[23] which is in line with this study where dryness was the individual symptom scored highest at baseline. Therefore, it is reasonable to recognize the eye dryness score as the potentially more appropriate tool to assess symptoms in DED studies. Patients with more severe baseline values for eye dryness score seemed to benefit most from CyclASol 0.1% treatment, echoing experience. This observation is also consistent with results reported from previous lifitegrast
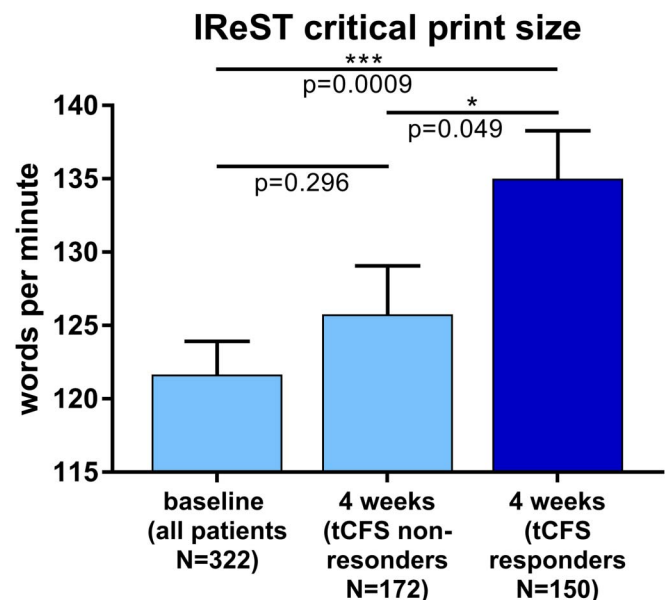
IReST critical print size

FIGURE 6. IReST critical print size in tCFS responder versus nonresponder. Reading speed improves statistically significantly for tCFS responders compared with nonresponders (*P* = 0.049) and compared with baseline (*P* = 0.0009). (The full color version of this figure is available at www.corneajrnl.com.)

TABLE 3. Treatment-Emergent AEs

	CyclASol 0.1%, n (%)	Vehicle, n (%)
Ocular and nonocular AEs		
No. of TEAEs	72	71
No. of subjects with at least one TEAE	49 (30.2)	45 (27.1)
No. of treatment-emergent serious AEs	0	3 (1.8)
No. of subjects discontinued treatment due to an AE	3 (1.9)	0
Ocular AEs*		
No. of TEAEs	31	23
No. of subjects with at least 1 TEAE	20 (12.3)	14 (8.4)
Ocular AEs* that occurred in more than 2% of patients		
Visual acuity reduced	5 (3.1)	3 (1.8)
Instillation site pain	4 (2.5)	2 (1.2)
Vision blurred	2 (1.2)	4 (2.4)

*Assessment relates to both eyes.

clinical studies, in which patients with moderate to severe symptoms experienced the larger symptom relief from active treatments.[24]

Reading is necessary for many important activities of daily living and leisure activities. Thus, difficulty with reading might contribute to lower quality of life. Reading impairment might also affect employment or decreased workplace productivity, particularly in individuals who work in an office setting.[25] Several investigations[10–12] have observed an increased impact of (central) corneal staining on reading speed, especially under straining conditions, thereby asserting CFS as a key parameter relevant to visual function. The central region seemed to especially benefit most from CyclASol 0.1% treatment in this study. Furthermore, the improvements in CFS scores were accompanied by increased visual function, as measured by IReST in this study. In the IReST critical print size test, patients showing an improvement of greater than or equal to 3 units in total CFS score (responders) showed an average and statistically significant increase of 13 wpm in reading speed at week 4 compared with those patients with less or no improvement in CFS score (nonresponders). Of further relevance to patients' quality of life related to visual function is the observation that a change of ≥10 wpm is considered clinically meaningful as a recognizable validated improvement for individual patients.[26,27]

The observed improvements in Schirmer test I scores reflect the known effect of cyclosporine A on tear production and are consistent with reported increase of tear production from other studies with cyclosporine A formulations that increase tear production after treatment. CyclASol 0.1% showed excellent safety, tolerability, and comfort profiles with 97% of the enrolled patients completing the treatment period. There were no meaningful imbalances among treatment groups in either ocular or nonocular TEAEs. Most TEAEs were mild or moderate in severity. In addition, the 2.5% rate of instillation site reactions was very low in comparison with rates reported for other DED treatments including lifitegrast and cyclosporine A containing formula-

tions.[15,16,24,28,29] Drop comfort assessments further support excellent tolerability.

One limitation of this study is the relatively short treatment duration. Therefore, long-term studies would be desirable to evaluate safety and tolerability and long term effects in patients with chronic DED. The inclusion of patients with predominantly aqueous-deficient DED could be arguably another limitation, which could confine the observed outcomes and restrict generalization to all forms of DED. On the other hand, cyclosporine's mode of action and previous data are corroborated in this study: patients with aqueous-deficient DED benefit most from treatment with CyclASol 0.1%.

CONCLUSIONS

In summary, the ESSENCE study demonstrated efficacy of CyclASol 0.1% ophthalmic solution on signs and symptoms of DED. Together with results from earlier studies, CyclASol 0.1% consistently showed clinically meaningful greater reductions in corneal and conjunctival staining and improvements in symptoms of dryness compared with those of its vehicle. Visual function improved with improvements in corneal staining. Safety and tolerability were excellent, with outstanding application comfort scores, reported usually only with lubricating eye drops rather than prescription DED medications.

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