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Long-Term Safety and Efficacy of a Water-Free Cyclosporine 0.1% Ophthalmic Solution for Treatment of Dry Eye Disease: ESSENCE-2 OLE

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Purpose: The ESSENCE-2 Open-Label Extension study aimed to demonstrate long-term safety, tolerability, and efficacy of a novel water-free, nonpreserved topical cyclosporine 0.1% ophthalmic solution (US brand name VEVYE) for patients with dry eye disease (DED).

Methods: This was a Phase 3, prospective, multicenter, open-label, clinical study. All patients received cyclosporine 0.1% ophthalmic solution and dosed each eye twice a day for 52 weeks. Primary safety end points were ocular and nonocular adverse events (AEs). Secondary safety end points included visual acuity, biomicroscopy, intraocular pressure, and dilated fundoscopy. Efficacy end points, such as total corneal fluorescein staining (tCFS) score (National Eye Institute [NEI] Scale), ocular symptoms (visual analog scale [VAS]), and Schirmer tear test, were also assessed.

Results: A total of 202 patients were enrolled from the ESSENCE-2 study. At week 52, 175 patients (86.6%) completed ESSENCE-2 open-label extension. A total of 55 patients (27.5%) reported 74 ocular treatment-emergent adverse events (TEAEs). The most common ocular AE was instillation site pain (6.5%), which was of mild intensity in all cases. Patients showed statistically significant improvements in all prespecified efficacy end points compared with baseline at each visit. Corneal staining improvements were early and stabilized over time while tear production improved continuously. Symptomatology improvement followed these effects with scores reaching a minimum after 1 year of treatment.

Conclusions: The water-free cyclosporine 0.1% ophthalmic solution was safe and well tolerated during long-term use. The results demonstrated sustained 1-year efficacy, in both signs and symptoms of DED, and may help understand short and long-term healing dynamics in a predominant inflammatory DED population.

Key Words: long-term study, DED, cyclosporine, corneal fluorescein staining, tolerability

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Dry eye disease (DED) management typically follows a staged approach based on severity and etiology.[1] When lifestyle changes, environmental adjustments, and use of artificial tears fail to provide adequate relief, a pharmacological therapy is recommended for patients with DED.[2] Topical cyclosporine is a preferred treatment option, targeting the chronic underlying ocular inflammation responsible for the clinical manifestation of DED and the related ocular surface damage.[1,3] Recently, a novel cyclosporine 0.1% ophthalmic solution (US brand name VEVYE by Harrow Eye, LLC, Nashville TN; development name CyclASol) received FDA approval for the treatment of signs and symptoms of DED in the United States. While cyclosporine is not water soluble, the novel water-free solvent perfluorobutylpentane (abbreviated F4H5) overcomes limitations of available formulation and forms a clear cyclosporine solution without oils, surfactants, and preservatives. These unique characteristics provide improved local bioavailability in the corneal epithelium, better efficacy on the ocular target tissue, and enhanced tolerability.[4–6] The only other ingredient of this water-free solution is ethanol in concentrations $<1\%$, which is within the regulatory accepted concentration range for ophthalmic products. The product and the vehicle have undergone an intense program of nonclinical pharmacokinetics, safety, and toxicology studies supporting its safe use.[5] There was no sign of ocular irritation or toxicity over 6 months of dosing in a toxicology study in rabbits using higher doses than in the

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clinical setting. Albeit local penetration of cyclosporine into the epithelium was enhanced in pharmacokinetic studies, aqueous humor concentrations of both cyclosporine and F4H5 were minimal, suggesting that both, as they are lipophilic compounds, do not pass the cornea.[7,8]

Previous randomized and controlled clinical studies (CYS-002, ESSENCE-1 [CYS-003], and ESSENCE-2 [CYS-004]) consistently demonstrated significant improvements in corneal and conjunctival staining with an onset of effect as early as after 2 and 4 weeks, respectively.[9–12] The rapid onset of effect and magnitude of effect are differentiators to existing cyclosporine treatments potentially caused by the novel vehicle. The safety and tolerability profile showed no significant imbalances between treatment groups with mainly mild ocular treatment-emergent adverse events (TEAEs) and a low proportion of instillation site reactions (approximately 8%).[13] Overall, these studies established the safety and efficacy of the water-free cyclosporine 0.1% ophthalmic solution over a treatment duration of up to 4 months.

This work presents the safety, tolerability, and efficacy results of the phase 3 study ESSENCE-2 open-label extension (OLE) using cyclosporine 0.1% ophthalmic solution in patients with DED over a 1-year treatment period as medications with rapid onset of action and good safety profile to address chronic inflammation and reduce complications associated with alternative treatment options remain an unmet need.

METHODS

Study Design

ESSENCE-2 OLE (CYS-005) was an open-label, single-arm extension study of ESSENCE-2 (CYS-004) to demonstrate the long-term safety, tolerability, and efficacy of a novel cyclosporine 0.1% ophthalmic solution. The study was performed at 14 clinical sites in the United States, in accordance with the Declaration of Helsinki, the Health Insurance Portability and Accountability Act of 1996, Good

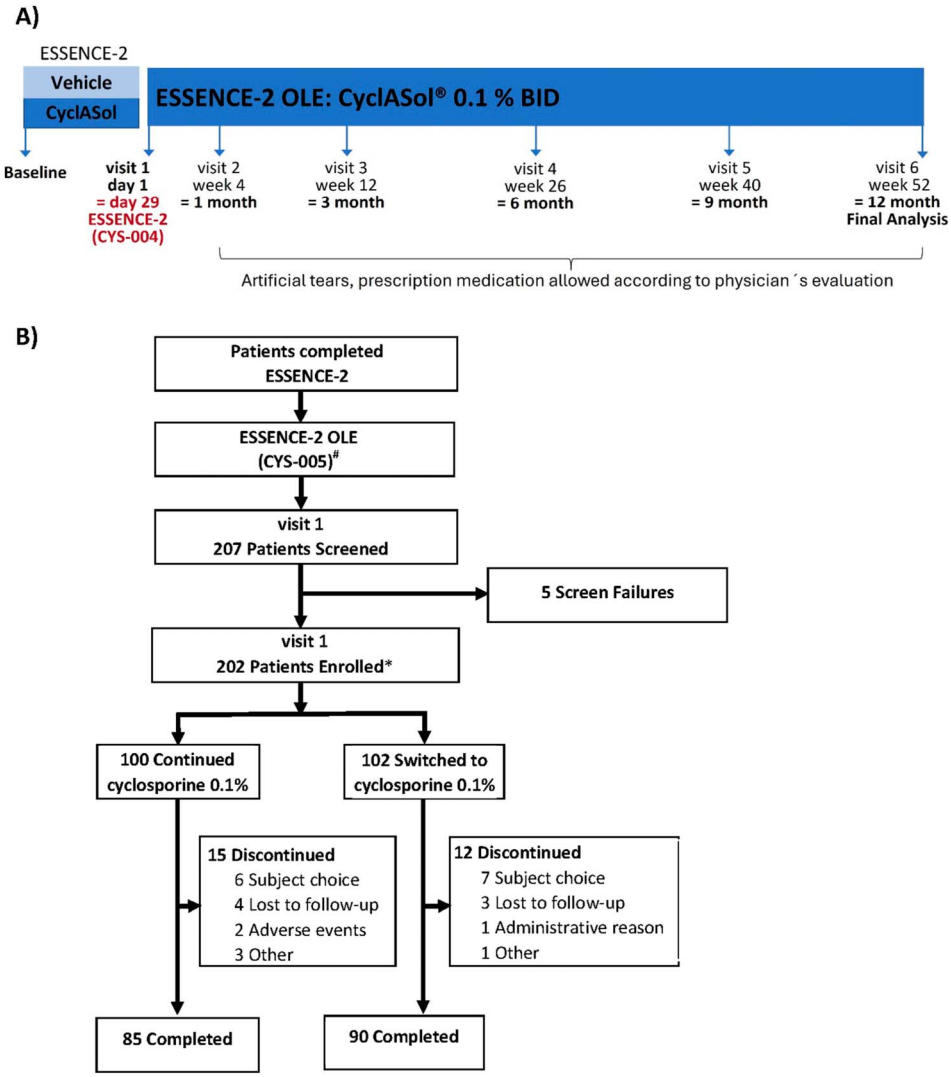

FIGURE 1. A, ESSENCE-2 OLE study design. B, Patient disposition. # The first 207 patients who completed ESSENCE-2 (both treatment arms) were screened for ESSENCE-2 OLE eligibility. A total of 202 enrolled patients comprised 100 patients who were randomized to cyclosporine 0.1% treatment during ESSENCE-2 and 102 patients who were randomized to the vehicle comparator during ESSENCE-2. *The safety analysis set comprised 200 subjects (98 subjects continued cyclosporine and 102 switched to cyclosporine) since 2 subjects were lost to follow-up directly after visit 1. BID, two times a day, OLE, open-label extension.

Clinical Practices guidelines, and all other applicable local and federal regulatory requirements and laws. The study was registered at ClinicalTrials.gov (NCT04523142) and reviewed and approved by the institutional review board Alpha IRB (San Clemente, CA).

Following informed consent, 202 patients who completed ESSENCE-2 and met all eligibility criteria were enrolled in the study to receive the cyclosporine 0.1% ophthalmic solution.

During the 52-week treatment period (Fig. 1A), patients administered a single drop of cyclosporine 0.1% ophthalmic solution in each eye twice daily. Safety, tolerability, and efficacy outcome measures were assessed at scheduled prespecified visits and interim telephone calls: visit 1 (day 1 = day 29 of ESSENCE-2), visit 2 (week 4), TC 1 (week 8), visit 3 (week 12), TC 2 (week 16), TC 3 (week 22), visit 4 (week 26), TC 4 (week 30), TC 5 (week 36), visit 5 (week 40), TC 6 (week 44), TC 7 (week 48), and visit 6 (week 52). The ESSENCE-2 baseline was also defined as baseline for this ESSENCE-2 OLE study.

Assessment of Outcome Measures

The primary safety end points at week 52 in this study included the assessment of ocular and nonocular AEs. TEAEs were defined as AEs occurring after the first dose of the study drug during ESSENCE-2 OLE. The investigator determined the severity and the relationship to the study drug.

Secondary safety end points included logMAR visual acuity (VA) assessed using the Early Treatment of Diabetic Retinopathy Study Scale (ETDRS) and slit-lamp biomicroscopy, which graded findings as normal or abnormal and described clinically relevant abnormal cases. Safety assessments further included intraocular pressure (IOP) assessed by contact tonometry and dilated fundoscopy, which graded findings as normal or abnormal and described clinically relevant abnormal cases. Acceptability of the study drug was assessed through 3 questions: "How satisfied are you with the study eye drop?" "How easy was the administration of the study eye drop?" and "How high is the likelihood that you would ask for prescription of the study eye drops?" Patients rated these questions on a scale from 0 (not) to 10 (very).

Efficacy was measured by change from baseline (CFB) (=ESSENCE-2 baseline) in total corneal fluorescein staining (tCFS) using fluorescein dye according to the National Eye Institute (NEI) Scale. The tCFS score was the sum of 5 corneal areas (inferior, superior, central, nasal, and temporal) graded from 0 to 3 per region (the higher the worse) and ranging from 0 to 15. The visual analog scale (VAS), which is a subject-reported symptom index, ranging from 0 = no discomfort to 100 = maximal discomfort, was used for parameters such as dryness score, frequency of dryness, awareness of dryness, blurred vision, reading problems, fluctuating vision, looking at screens, and driving at night. In addition, efficacy was evaluated for tear production as mm of wetting at 5 minutes compared with baseline using the unanesthetized Schirmer tear test I. The proportion of tCFS responders was defined as an improvement of 3 grades or more from baseline on the NEI Scale. In addition, conjunctival staining was evaluated using lissamine green dye according to the Oxford grading scale, with the sum of 2 areas (nasal and temporal) graded from 0 to 5 per region, with higher scores indicating worse conditions and ranging from 0 to 10. Treatment compliance was assessed based on patient dosing diaries, with compliance defined as self-administering 80% or more of the expected doses. The study eye for efficacy analysis was determined during ESSENCE-2 based on the eye with the highest tCFS score at baseline. Ocular symptoms were assessed per patient.

Patients

Patients were eligible for the study if they met all of the following inclusion criteria: 1) completion of the clinical study ESSENCE-2; 2) diagnosis of DED at visit 1 of ESSENCE-2; 3) compliance with study procedures and application of IMP; 4) provision of written informed consent; and 5) willingness and ability to follow instructions, including participation in all study assessments and visits. Key exclusion criteria included clinically relevant abnormal slit-lamp findings, including lid, conjunctival, or corneal abnormalities. Patients unwilling to refrain from wearing contact lenses or those with planned ocular or lid surgery were also excluded from the study. Use of artificial tears was permitted after visit 2 (week 4), and other concomitant ocular DED treatments were allowed only after unsuccessful attempt with artificial tears. Topical prescription medications were permitted as per physicians' evaluation.

Statistical Methods

The safety analysis set (SAF) population included all enrolled patients who had received at least 1 dose of the study drug. All safety and efficacy assessments were analyzed using data from the SAF, and summary statistics were calculated by visit. The sample size of at least 100 evaluable patients at week 52 was selected based on regulatory and ICH (International Council for Harmonization) guidance. This sample size was chosen to achieve a >95% probability to observe AEs that occur at an incidence rate of at least 3%.

RESULTS

Patient Disposition

The first patient rolled over from the ESSENCE-2 study on January 04, 2021, and the last patient completed the study on April 30, 2022. Fourteen clinical sites screened 207 patients and enrolled 202. Of those, 100 patients were randomized during ESSENCE-2 to the cyclosporine group ("continued cyclosporine 0.1%" in ESSENCE-2 OLE) and 102 patients were previously randomized to the vehicle group ("switched to cyclosporine 0.1%" in ESSENCE-2 OLE) (Fig. 1B). The SAF comprised 200 patients (98 patients continued cyclosporine, and 102 switched to cyclosporine) since 2 patients were lost to follow-up immediately after visit 1.

A total of 175 patients (86.6%) completed the study, while 27 patients (13.4%) discontinued their participation. Fifteen patients (15%) belonged to the "continued cyclosporine group," and 12 patients (11.8%) belonged to the "switched to cyclosporine" group. The main reasons for study discontinuation were patient choice (13 patients), lost to follow-up (7 patients), AEs (2 patients), administrative reasons (1 patient), and other reasons, such as planned surgery (1 patient), eye surgery (1 patient), investigator decision (1 patient), and pregnancy (1 patient).

A large proportion of ESSENCE-2 OLE patients (92.5%) were compliant with the study medication. Overall, 25 patients (12.5%) used ocular concomitant medications during the ESSENCE-2 OLE study. The most frequent group among these was nutritional supplements for ocular health, used by 13 patients (6.5%). Artificial tears, permitted after week 4, were only used by 6 patients (3%).

Demographic and Baseline Characteristics

Demographic and baseline disease characteristics were well balanced between patients who continued with cyclosporine and those who switched to cyclosporine (Table 1). The study population had a mean age of 59 ± 14.8 years, and 83 patients (41.5%) were 65 years and older. Most patients were female (74.0%). Most patients self-identified with the following race: 17 Asian (8.5%), 27 Black or African American (13.5%), and 153 White (76.5%).

At baseline (=ESSENCE-2 baseline), the mean [SD] tCFS score was 11.6 [1.47] and conjunctival staining was 3.9 [1.80]. The mean for the Schirmer tear test at baseline was 4.7 [2.78] mm. Patients were highly symptomatic with a dryness score of 70.4 [12.99] and a blurred vision score of 53.6 [25.74].

Safety

TEAEs (ocular and nonocular) that occurred after the first administration of the study drug during ESSENCE-2 OLE were reported by 48.5% of patients during the study period. Thirty-four percent of patients experienced TEAEs that were mild, 13.5% of patients had moderate TEAEs, and only 1% reported TEAEs that were severe in intensity. Ocular TEAEs were reported by 27.5% of patients, from which 50 of 55 cases were classified as mild. Only 1 patient who continued cyclosporine treatment had a severe ocular TEAE (macular pucker) that was not suspected to be related to the study drug. The most common ocular TEAEs were instillation site pain in 13 patients (6.5%), vitreous detachment in 9 patients (4.5%), and reduced VA in 6 patients (3.0%). All other eye disorders occurred in less than 2% of the patients. Reporting of instillation site pain decreased over the study period.

There were no meaningful imbalances between patients who previously received vehicle and patients who previously received cyclosporine in the ESSENCE-2 study in either ocular TEAEs (25 [24.5%] vs. 30 [30.6%]) or nonocular TEAEs (32 [31.4%] vs. 30 [30.6%]).

Seven serious TEAEs were reported during the study by 4 patients (2%) (2 continued cyclosporine and 2 switched to cyclosporine). All serious adverse events were nonocular, assessed as unrelated and resolved by the end of the study.

Three patients continued cyclosporine in ESSENCE-2 OLE-discontinued study treatment due to an AE (2 nonocular; 1 ocular [mild ocular burning after IMP instillation]). No deaths occurred during the study (Table 2).

TABLE 1. Demographic and Baseline Characteristics

	n (%)		
Demographic	**Patients Who Continued Cyclosporine (N = 98)**	**Patients Who Switched to Cyclosporine (N = 102)**	**All Patients (N = 200)**
Mean age (SD)	59.0 (14.69)	59.1 (14.93)	59.0 (14.78)
≥65 yrs (%)	39 (39.8)	44 (43.1)	83 (41.5)
Women (%)	72 (73.5)	76 (74.5)	148 (74.0)
Race (%)			
Asian	9 (9.2)	8 (7.8)	17 (8.5)
Black or African American	15 (15.3)	12 (11.8)	27 (13.5)
White	73 (74.5)	80 (78.4)	153 (76.5)
Baseline ocular characteristics		**Mean (SD)**	
tCFS (NEI)	11.5 (1.46)	11.6 (1.48)	11.6 (1.47)
Lissamine	3.9 (1.86)	3.9 (1.76)	3.9 (1.80)
Unanesthetized Schirmer I	4.8 (2.83)	4.6 (2.74)	4.7 (2.78)
VAS severity of dryness	70.3 (12.82)	70.5 (13.21)	70.4 (12.99)
VAS blurred vision at baseline	53.7 (24.94)	53.4 (26.61)	53.6 (25.74)
VA (logMAR)*	0.113 (0.1664)	0.111 (0.1529)	0.112 (0.1592)
IOP, mm Hg*	15.6 (2.95)	15.5 (3.07)	15.5 (3.00)

*ESSENCE-2 baseline values for VA and IOP.
Lissamine, conjunctival lissamine green staining (Oxford).

TABLE 2. Summary of TEAEs

	n (%)		
	Patients Who Continued Cyclosporine (N = 98)	**Patients Who Switched to Cyclosporine (N = 102)**	**All Patients (N = 200)**
AEs			
TEAEs	93	117	210
Patients with at least 1 TEAE (%)	46 (46.9)	51 (50.0)	97 (48.5)
Suspected related to study drug (%)	13 (13.3)	7 (6.9)	20 (10)
Treatment-emergent SAEs	3	4	7
Patients with at least 1 treatment-emergent SAE (%)	2 (2.0)	2 (2.0)	4 (2.0)
Patients discontinued treatment due to an AE	3	0	3
Ocular AEs			
TEAEs	32	42	74
Patients with at least 1 TEAE (%)	30 (30.6)	25 (24.5)	55 (27.5)
Mild (%)	28 (28.6)	22 (21.6)	50 (25.0)
Moderate (%)	1 (1.0)	3 (2.9)	4 (2.0)
Severe (%)	1 (1.0)	0	1 (0.5)
Ocular adverse events that occurred in more than 2% of patients (%)			
Vitreous detachment	4 (4.1)	5 (4.9)	9 (4.5)
Visual acuity reduced	5 (5.1)	1 (1.0)	6 (3.0)
Posterior capsule opacification	1 (1.0)	2 (2.0)	3 (1.5)
Instillation site pain	7 (7.1)	6 (5.9)	13 (6.5)

SAE, serious adverse event; TEAEs, treatment-emergent adverse events.

For all patients, no significant changes from baseline were observed in mean values for slit-lamp biomicroscopy, dilated fundoscopy, VA, or IOP. Slit-lamp assessments at all visits showed no shifts to abnormal clinically significant findings from the normal baseline during the 52-week follow-up.

Approximately 91% of patients rated the acceptability question "How satisfied are you with the study eye drop?"

TABLE 3. Efficacy Measures of ESSENCE-2 OLE

	CyclASol 0.1% to CyclASol 0.1% (N = 98)	**Vehicle to CyclASol 0.1% (N = 102)**	**All (N = 200)**
	CFB mean (SD), *P**		
tCFS day 1	−4.8 (3.04), <0.0001	−4.0 (3.31), <0.0001	−4.4 (3.20), <0.0001
Week 4	−5.8 (2.87), <0.0001	−5.5 (3.12), <0.0001	−5.6 (3.00), <0.0001
Week 12	−6.1 (2.72), <0.0001	−6.0 (3.14), <0.0001	−6.0 (2.94), <0.0001
Week 26	−6.1 (3.00), <0.0001	−5.8 (3.05), <0.0001	−5.9 (3.02), <0.0001
Week 52	−5.8 (2.83), <0.0001	−5.4 (3.54), <0.0001	−5.6 (3.21), <0.0001
Lissamine day 1	−1.7 (1.74), <0.0001	−1.0 (1.37), <0.0001	−1.4 (1.60), <0.0001
Week 4	−1.7 (1.86), <0.0001	−1.1 (1.75), <0.0001	−1.4 (1.82), <0.0001
Week 12	−1.6 (1.89), <0.0001	−1.4 (1.99), <0.0001	−1.5 (1.94), <0.0001
Week 26	−1.8 (1.81), <0.0001	−1.6 (1.99), <0.0001	−1.7 (1.90), <0.0001
Week 52	−1.5 (1.95), <0.0001	−1.5 (1.94), <0.0001	−1.5 (1.94), <0.0001
Dryness score day 1	−15.8 (27.39), <0.0001	−16.3 (24.90), <0.0001	−16.0 (26.09), <0.0001
Week 4	−18.4 (25.70), <0.0001	−13.1 (23.21), <0.0001	−15.6 (24.52), <0.0001
Week 12	−19.8 (25.80), <0.0001	−12.7 (24.60), <0.0001	−16.1 (25.37), <0.0001
Week 26	−22.9 (25.83), <0.0001	−22.3 (26.68), <0.0001	−22.6 (26.20), <0.0001
Week 52	−26.6 (27.24), <0.0001	−24.2 (25.62), <0.0001	−25.4 (26.37), <0.0001
Blurred vision day 1	−7.5 (25.02), 0.0038	−5.2 (24.65), 0.0371	−6.3 (24.79), 0.0004
Week 4	−9.5 (26.77), 0.0009	−10.6 (27.41), 0.0002	−10.1 (27.03) <0.0001
Week 12	−9.4 (25.00), 0.0005	−6.0 (28.07), 0.0366	−7.6 (26.62), <0.0001
Week 26	−11.7 (24.67), <0.0001	−9.6 (31.14), 0.0038	−10.6 (28.16), <0.0001
Week 52	−15.7 (28.37), <0.0001	−12.6 (30.42), 0.0002	−14.1 (29.40), <0.0001

*Baseline = ESSENCE-2 baseline, *P*-value = paired *t* test.

with a score of 5 or higher on a 0 to 10 scale (the higher the better), indicating most patients were satisfied with the treatment. In addition, 33.1% of patients provided the highest possible rating of 10.

Efficacy

During the ESSENCE-2 OLE extension study, all prespecified efficacy parameters demonstrated statistically significant improvements compared with baseline in ESSESNCE-2 at all visits (Table 3).

Furthermore, most sign and symptom end points continued to improve and reached statistical significance compared with visit 1 of ESSENCE-2 OLE at visit 6/week 52 (Figs. 2A–F).

At day 1, the first visit in this study, and at the last visit of ESSENCE-2, the sign efficacy end points of CFB in the total CFS score (NEI Scale) and conjunctival lissamine green staining score (Oxford scale) showed higher improvements in the group that received cyclosporine during ESSENCE-2 than in the group that received vehicle, which is the treatment effect of cyclosporine in ESSENCE-2 (Table 3). Subsequently, tCFS continued to improve at week 4 compared with day 1, with a more pronounced effect in the group that switched to cyclosporine (mean CFB [SD] to V1 in corneal staining −1.1 [3.41] vs. −1.5 [3.15]). The staining remained stable at a low level from week 4 onwards, and this effect was maintained throughout the 52-week observation period (Figs. 2A, B). Statistically significant improvements in CFB of corneal staining could be observed in all 5 subregions (see Table, Supplemental Digital Content 1, http://links.lww.com/ICO/B673).

The proportion of responders in tCFS at day 1 of ESSENCE-2 OLE was 79% for patients who continued cyclosporine versus 68% for patients who switched to cyclosporine, showing the treatment effect of cyclosporine during ESSENCE-2. At 4 weeks, patients switching to cyclosporine during the extension study achieved the same level of improvement as the group that continued with cyclosporine, showing the treatment effect of cyclosporine during ESSENCE-2 OLE. The tCFS responder rates remained

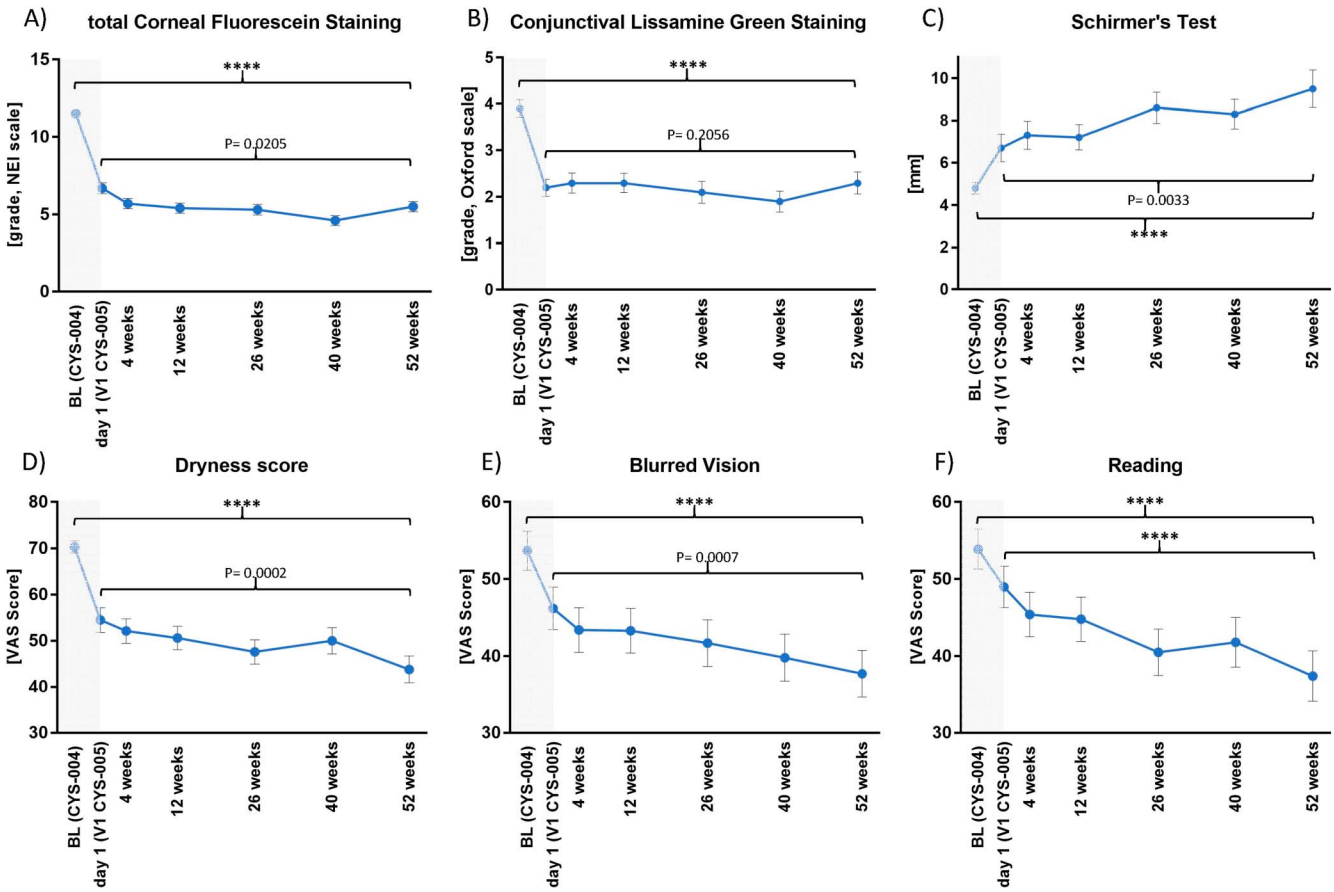

FIGURE 2. Mean values with SEM of sign and symptom improvement over 52 weeks for cyclosporine 0.1%-treated subjects in A, tCFS; B, conjunctival lissamine green staining; C, Schirmer test; D, dryness score using the VAS; E, blurred vision (VAS); and F, reading impairment (VAS). *P*-values show significance of improvements at week 52 compared with day 1 or CYS-004 baseline; gray area: data from ESSENCE-2 (CYS-004) study; D29 ESSENCE-2, day 1 ESSENCE-2 OLE; ^{P}*P*-value, paired *t* test; ****$P < 0.0001$.

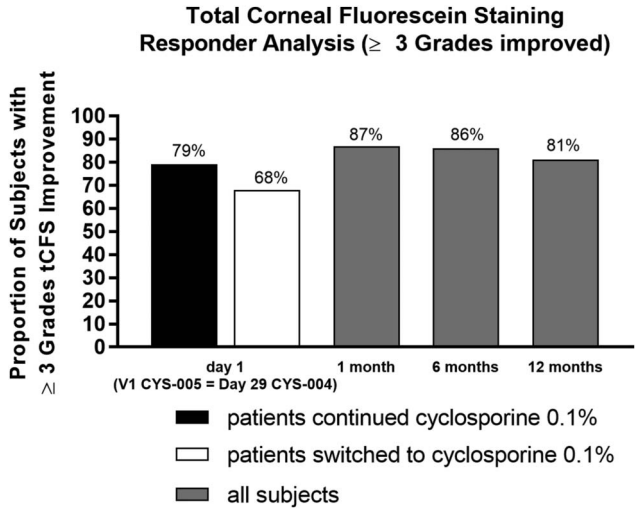

FIGURE 3. tCFS responder analysis of the proportion of corneal fluorescein staining responders over 52 weeks (≥3 score improvement on the NEI Scale from ESSENCE-2 baseline) visualized at day 29 for patients continuing cyclosporine 0.1% versus patients switching to cyclosporine 0.1% and up to 12 months for all patients.

around 80% for all visits throughout the 52-week observation period (Fig. 3).

Mean Schirmer tear test scores measuring tear production showed statistically significant improvements from baseline in patients who continued cyclosporine. The treatment effect increased over the course of the ESSENCE-2 OLE study and reached statistical significance over visit 1 starting after 26 weeks of treatment (Fig. 2C; 26 weeks, $P = 0.0361$; 52 weeks, $P = 0.0033$). The average tear film breakup time was 3.37 seconds at baseline in patients who continued cyclosporine, and it statistically significantly improved to 3.82 seconds at Visit 1 and stabilized at around 4 seconds at subsequent visits.

In patients receiving continued treatment with cyclosporine, all symptom scores assessed with the VAS improved over the course of the study, reaching their minimum at the 52-week visit (dryness, blurred vision, and reading, as shown in Figs. 2D–F). A similar pattern was observed for the total OSDI score with a mean score of 46.5 at baseline in patients who continued cyclosporine and reaching its minimum of 31.2 at the 52-week visit. These VAS and OSDI symptom scores were statistically significant from baseline at each visit and also significantly improved over visit 1 of ESSENCE-2 OLE at the last visit.

DISCUSSION

The open-label study ESSENCE-2 OLE (CYS-005) assessed the long-term safety, tolerability, and efficacy of a novel water-free cyclosporine 0.1% ophthalmic solution (US brand name VEVYE, Novaliq development name CyclASol) in patients who completed ESSENCE-2 (CYS-004). A low average Schirmer tear production test score and high average corneal staining and ocular symptom scores at baseline characterized the study population as patients with moderate-to-severe predominantly aqueous-deficient DED. The 52-week treatment duration in ESSENCE-2 OLE provided valuable insight into the extended use of this product. Patients already randomized to cyclosporine during ESSENCE-2 were exposed to the treatment for cumulative 56 weeks.

The study demonstrated a favorable safety profile for the cyclosporine 0.1% ophthalmic solution, with no increase or imbalance in AE rates for patients switching from vehicle to active. Ocular TEAEs were mostly of mild intensity, and the rate of TEAEs suspected to be related to the study drug was low (10%). Instillation site pain, the most common ocular TEAE, occurred in 6.5% of patients and was of mild severity in all cases. This rate is slightly lower than in the preceding ESSENCE-2 study, which showed mild instillation site reactions in about 10% of patients in the active group,[11,12] and higher than in the ESSENCE-1 study, which showed such reaction only in about 2.5% of cyclosporine-treated patients.[10] These higher rates of instillation site reaction in the ESSENCE-2/ESSENCE 2-OLE studies might be related to the concurrent SARS-COV-2 pandemic and face mask mandates, which might had confounded this end point.[14] Safety assessments of slit-lamp biomicroscopy and dilated fundoscopy in VA and IOP were unremarkable. A great proportion of patients (>90%) were satisfied with the treatment after 1 year.

These findings are consistent with results from the previous studies CYS-002 (4 months), ESSENCE-1 (3 months), and ESSENCE-2 (1 month)[9–11] and further confirm the good safety and tolerability profile of this water-free cyclosporine 0.1% ophthalmic solution. The favorable tolerability profile potentially explains the high proportion of compliant patients (92.5%) and those completing the 52-week observation period (86.6%), surpassing rates reported for other DED treatments.[10,15,16]

As DED is often described as chronic and progressive,[3] patient compliance is highly associated with their treatment success. Real-world data suggest that the proportion of patients continuing treatment with available medications at 12 months is low: 31.7% for lifitegrast and 27.5% for cyclosporine 0.05% emulsion.[17] Although discontinuation reasons were not captured, the authors speculate that installation site reactions, long-term use of preservatives, and late onset of efficacy are the key reasons for treatment discontinuation.

The ESSENCE-2 OLE study demonstrated maintenance of effect as well as continuous improvements on signs and symptoms of DED up to cumulative 56 weeks. Patients who switched from vehicle to cyclosporine treatment in ESSENCE-2 OLE showed more pronounced improvements in ocular surface outcomes in the 4 weeks, achieving similar levels of improvement as the group that already received cyclosporine in ESSENCE-2. A similar level of improvement was also observed in the ESSENCE-1 study, which was similarly designed as the ESSENCE-2 study. This confirms the fast onset of action of the water-free cyclosporine 0.1% ophthalmic solution observed in previous studies, differing from other DED prescription

medications.[18–23] After 4 weeks, more than 80% of all patients showed a clinically meaningful improvement of ≥3 grades in the tCFS score,[11] which was sustained throughout the study, underlining that a large proportion of patients benefit from the therapy.

Patients with an average Schirmer test score of 5 mm at baseline demonstrated significant and clinically meaningful improvements reaching an average of about 10 mm after 56 weeks of treatment. These values are considered normal and reflect the beneficial effect of cyclosporine on tear production.[1,24]

Importantly, ocular symptoms as measured via the VAS and OSDI improved throughout the study, achieving a minimum at the end of the observation period. These improvements were statistically significant at all visits compared with baseline, and most symptoms also significantly improved compared with visit 1. This indicates that the effect on patients' symptoms lags behind the healing effect on the ocular surface. Symptomatic response in patients with DED often differs from clinically treatment effects, which might be influenced by corneal nerve participation.[25]

The ongoing inflammation of the impaired ocular surface as commonly present in patients with DED leads to sensitization of the somatosensory pathways and hypersensitive corneal nerves.[26] This phenomenon might explain why some patients continue to experience ocular discomfort symptoms despite the treatment's positive impact on the ocular surface. A study conducted by Galor et al[27] reported a lack of symptom improvement after topical treatment in patients with DED. Even though the ocular surface was successfully treated, the ocular discomfort symptoms persisted for an extended period.

Cyclosporine's neuroprotective features in DED may play a crucial role in supporting the healing of damaged nerves.[25,28] This could account for the observed continued improvement in symptom parameters over the 56-week period. In addition, the steady improvement in tear production may also contribute to the dynamics of symptom improvement.

The water-free cyclosporine 0.1% ophthalmic solution demonstrated favorable long-term efficacy, safety, and tolerability, addressing an unmet medical need in DED therapy, potentially increasing patient adherence to treatment. The main limitation of this study was the treatment of all patients with cyclosporine and comparator data not being available for this extended observation period. In addition, focusing on patients with moderate-to-severe DED excluded mild cases from being studied over a long time period.

We conclude that the ESSENCE-2 OLE study provides robust evidence that the novel water-free cyclosporine 0.1% ophthalmic solution is safe and well tolerated for long-term use and overcomes limitations of available DED formulations. The improvement in signs and symptoms demonstrate sustained efficacy in DED over the 52-week observation period. The presented data may create awareness for the short and long-term healing dynamics in a predominant inflammatory population of this chronic condition.

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